

STUDIES OF REACTIONS INVOLVING ELECTRON TRANSFER  
OF  
ORGANOCUPRATE REAGENTS

A THESIS

Presented to

The Faculty of the Division of Graduate Studies

By

Joyce Marie Wilkins

In Partial Fulfillment  
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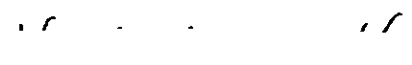
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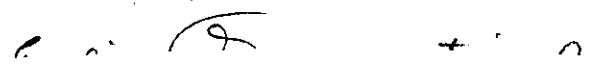
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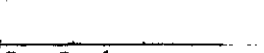
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## SUMMARY

Chapter I.      A SURVEY OF THE REACTION OF VARIOUS LITHIUM  
DIORGANOCUPRATES WITH ENONES

The reactions of various lithium diorganocuprate reagents ( $R_2CuLi$ ) with a series of enones having different reduction potentials have been studied. With difficultly reduced enones, the ability of the various cuprates,  $R_2CuLi$ , to give good yields of conjugate addition products lies in the order:  $n-Bu_2CuLi > (vinyl)_2CuLi \sim Ph_2CuLi > sec-Bu_2CuLi \sim Me_2CuLi > t-Bu_2CuLi > (allyl)_2CuLi$ . The limiting enone reduction potentials needed to obtain satisfactory yields of conjugate addition products with the various cuprate reagents are: -2.35 to -2.4V for  $n-Bu_2CuLi$ ,  $(vinyl)_2CuLi$ , and  $Ph_2CuLi$ ; -2.3 to -2.35V for  $sec-Bu_2CuLi$  and  $Me_2CuLi$ ; -2.1V for  $t-Bu_2CuLi$ ; and -2.0 to -2.1V for  $(allyl)_2CuLi$ .

Chapter II.     THE EFFECT OF SOLVENT ON THE CONJUGATE ADDITION  
OF LITHIUM DIORGANOCUPRATES TO ENONES

The reactions of  $Me_2CuLi$  with a series of enones of increasingly negative reduction potential have been studied. With difficultly reduced enones, the yield of the conjugate adduct is diminished and a substantial fraction of the enone is converted to its metal enolate. For a given enone, the best yield of conjugate adduct is obtained in a non-polar solvent ( $Et_2O$ -pentane mixture)

and becomes progressively poorer as the solvent becomes more polar; the order of solvents for the optimum yield of conjugate adduct is:  $\text{Et}_2\text{O-pentane} > \text{Et}_2\text{O-PhH} > \text{Et}_2\text{O} > \text{Et}_2\text{O-THF}$  or  $\text{Et}_2\text{O-DME} > \text{Et}_2\text{O-DMF}$ . The limiting enone reduction potentials for satisfactory yields of conjugate adducts is  $-2.35\text{V}$  in  $\text{Et}_2\text{O-pentane}$  mixtures,  $-2.2\text{V}$  in  $\text{Et}_2\text{O-THF}$  or  $\text{Et}_2\text{O-DME}$  mixtures, and less negative than  $-2.0\text{V}$  in  $\text{Et}_2\text{O-DMF}$  mixtures. Thus, the reactivity of  $\text{Me}_2\text{CuLi}$  in conjugate addition reactions can be controlled by selection of an appropriate reaction solvent.

### Chapter III.

#### Part A. THE NATURE OF THE ENOLATE FORMED BY ADDITION OF LITHIUM DIMETHYLCUPRATE TO ENONES

The conjugate addition of  $\text{Me}_2\text{CuLi}$  to 3-methyl-2-cyclohexenone resulted in the formation, prior to hydrolysis, of a lithium enolate rather than some other intermediate in which the enolate was associated with a copper (I) species. Supportive evidence concerning this intermediate was obtained from the following information. (1) A  $^{13}\text{C}$  NMR spectrum of the product in  $\text{Et}_2\text{O}$  solution indicates the presence of the lithium enolate. (2) An enol acetate was formed by reaction of the intermediate with  $\text{Ac}_2\text{O}$ . Treatment of the enol acetate with 2 equiv. of  $\text{MeLi}$  afforded an  $\text{Et}_2\text{O}$  solution of the lithium enolate whose  $^{13}\text{C}$  NMR spectrum corresponded to the spectrum of the solution obtained from the cuprate reaction. (3) A copper analysis indicated that more than 99% of all the copper employed in the reaction was in the  $(\text{MeCu})_n$  precipitate rather than in the solution



containing the metal enolate.

### Chapter III.

#### Part B. REACTION OF LITHIUM DIMETHYLCUPRATE WITH ALKYL ARYL KETONES

This section describes several reactions of organocuprate reagents and electrochemical measurements of aryl alkyl ketones and enones that were part of a general study of aryl alkyl ketones with cuprate reagents.

The reaction of t-butyl phenyl ketone with  $\text{Me}_2\text{CuLi}$  was studied. In addition, a competition experiment was performed to obtain an estimate of the relative rate at which  $\text{Me}_2\text{CuLi}$  reacts with two enones with different reduction potentials.

### Chapter III.

#### Part C. A CONVENIENT PRECURSOR FOR THE GENERATION OF LITHIUM ORGANOCUPRATES

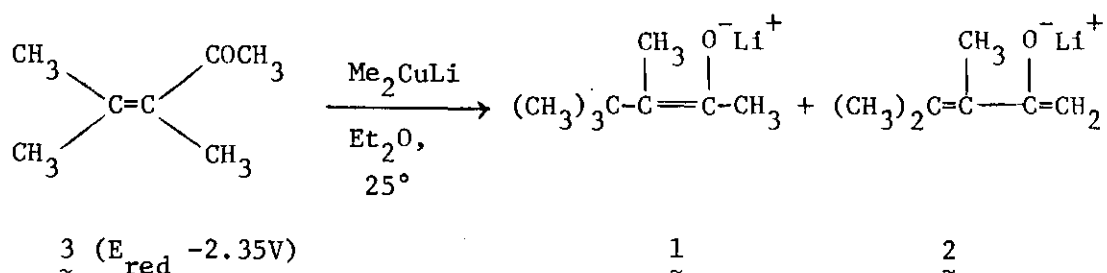
To avoid side reactions resulting from the presence of  $\text{Cu(II)}$  compounds and other metal salt impurities in the  $\text{Cu(I)}$  salts used to form lithium organocuprate reagents, use of the easily prepared, crystalline complex,  $\text{Me}_2\text{SCuBr}$  was developed.

This section examines several procedures for the preparation of lithium divinylcuprate and the use of this reagent for the conjugate addition of a vinyl group to an unsaturated ketone. The reactions described are part of a more general study of the formation and use of cuprate reagents.

## CHAPTER I

A SURVEY OF THE REACTION OF VARIOUS LITHIUM  
DIORGANOCUPRATES WITH ENONESIntroduction and Discussion

Previous study<sup>1</sup> of the reaction of lithium dimethylcuprate ( $\text{Me}_2\text{CuLi}$ ) with various  $\alpha,\beta$ -unsaturated carbonyl compounds in ether solution has indicated a correlation between the reduction potential ( $E_{\text{red}}$ ) of the unsaturated carbonyl compound and the success of conjugate addition of  $\text{Me}_2\text{CuLi}$ . In particular, unsaturated carbonyl compounds with  $E_{\text{red}}$  values less negative than  $-2.3\text{V}$  (vs sce in an aprotic solvent) normally react with  $\text{Me}_2\text{CuLi}$  in  $\text{Et}_2\text{O}$  solution to form the conjugate addition product in good yield. As the  $E_{\text{red}}$  value of the unsaturated carbonyl compound (e.g. 3) becomes more negative than  $-2.3\text{V}$ , the yield of the conjugate adduct (e.g. 1) is diminished and the remaining unsaturated carbonyl compound either fails to react or reacts with the  $\text{Me}_2\text{CuLi}$  to form  $\text{CH}_4$  and an enolate ion (e.g. 2) that remains in the reaction mixture until hydrolysis. In such cases, the proportion of conjugate adduct 1 is increased by the use of a less polar solvent (e.g.  $\text{Et}_2\text{O}$ -pentane) and is diminished by the use of a polar solvent (e.g. THF or DME).<sup>1g</sup> A less common side reaction occasionally observed<sup>1</sup> when conjugate addition



is inhibited is a rather slow 1,2-addition of the cuprate to the carbonyl group to form an alcohol by-product. Although the formation of alcohol by-products accompanying the products of conjugate addition are reported rather frequently in the utilization of  $\text{Me}_2\text{CuLi}$  in various synthetic operations, we are inclined to believe that many of these alcohol by-products are the result of insufficient care on the part of the experimenter to ensure that no excess  $\text{MeLi}$  was present in the  $\text{Me}_2\text{CuLi}$  reagent. This difficulty arising from excess  $\text{MeLi}$  is aggravated by the use of low reaction temperatures ( $-60$  to  $-70^\circ$ ) because ethereal solutions of  $\text{Me}_2\text{CuLi}$  frequently fail to react with enones to form conjugate addition or enolate products at temperatures below  $-30$  to  $-40^\circ$  while  $\text{MeLi}$  will often add to carbonyl groups at  $-60$  to  $-70^\circ$  to form 1,2-addition products.

Correlation between successful conjugate addition and enone  $\text{E}_{\text{red}}$  values of  $-2.3\text{V}$  or less provides a useful way to predict whether desired conjugate addition reactions of ethereal  $\text{Me}_2\text{CuLi}$  are likely to be successful. However, there is no reason to believe that the same limiting  $\text{E}_{\text{red}}$  value ( $-2.3\text{V}$ ) will be applicable either to other lithium diorganocuprates ( $\text{R}_2\text{CuLi}$ ,  $\text{R} \neq \text{Me}$ ) since  $\text{E}_{\text{red}}$  varies even with solutions of  $\text{Me}_2\text{CuLi}$  in solvents other

than  $\text{Et}_2\text{O}$ .<sup>1g</sup> In order to examine the question of limiting  $E_{\text{red}}$  values for successful conjugate addition with various cuprate reagents  $\text{R}_2\text{CuLi}$ , we have selected a set of structurally similar enones 3-5 (see Table I-1) whose  $E_{\text{red}}$  values vary from -2.08V to -2.35V, which is the typical range of  $E_{\text{red}}$  values for enones with alkyl substituents.<sup>3</sup> This set of enones 3-5 was used to survey reactions with the various cuprates 6-12 as solutions in  $\text{Et}_2\text{O}$  or in  $\text{Et}_2\text{O}$ -hexane mixtures. In performing these reactions we selected reaction temperatures 5-10° below the temperature at which significant thermal decomposition of the cuprate reagent takes place. In successful conjugate addition reactions only 1 mol equiv of  $\text{R}_2\text{CuLi}$  reagent is required for each mol equiv of enone.<sup>4</sup> However, for this reaction survey, we used an excess of each  $\text{R}_2\text{CuLi}$  reagent in order to minimize the possibility that the starting enones 3-5 were recovered because of adventitious destruction of a portion of the  $\text{R}_2\text{CuLi}$  reagent. The results of this survey of cuprate-enone reactions are summarized in Table I-1. The product yields were determined either by isolation or by glpc analysis employing a suitable internal standard and calibrated glpc apparatus. In each case samples of the indicated products were isolated and characterized (see Experimental Section) to confirm their identities.

Based upon the results summarized in Table I-1, the order of general reactivity for conjugate addition of the various cuprates is:  $(\text{n-Bu})_2\text{CuLi} > (\text{CH}_2=\text{CH})_2\text{CuLi} \sim \text{Ph}_2\text{CuLi} > (\text{sec-Bu})_2\text{CuLi} \sim \text{Me}_2\text{CuLi} > (\text{t-Bu})_2\text{CuLi} > (\text{CH}_2=\text{CHCH}_2)_2\text{CuLi}$ . In other studies where mixtures of cuprates such as  $\text{Me}_2\text{CuLi} + (\text{CH}_2=\text{CH})_2\text{CuLi}$  [or the mixed reagent

Table I-1. Reaction of  $R_2CuLi$  Reagents With the Enones 3-5 in  $Et_2O$  or  $Et_2O$ -Hexane Solution

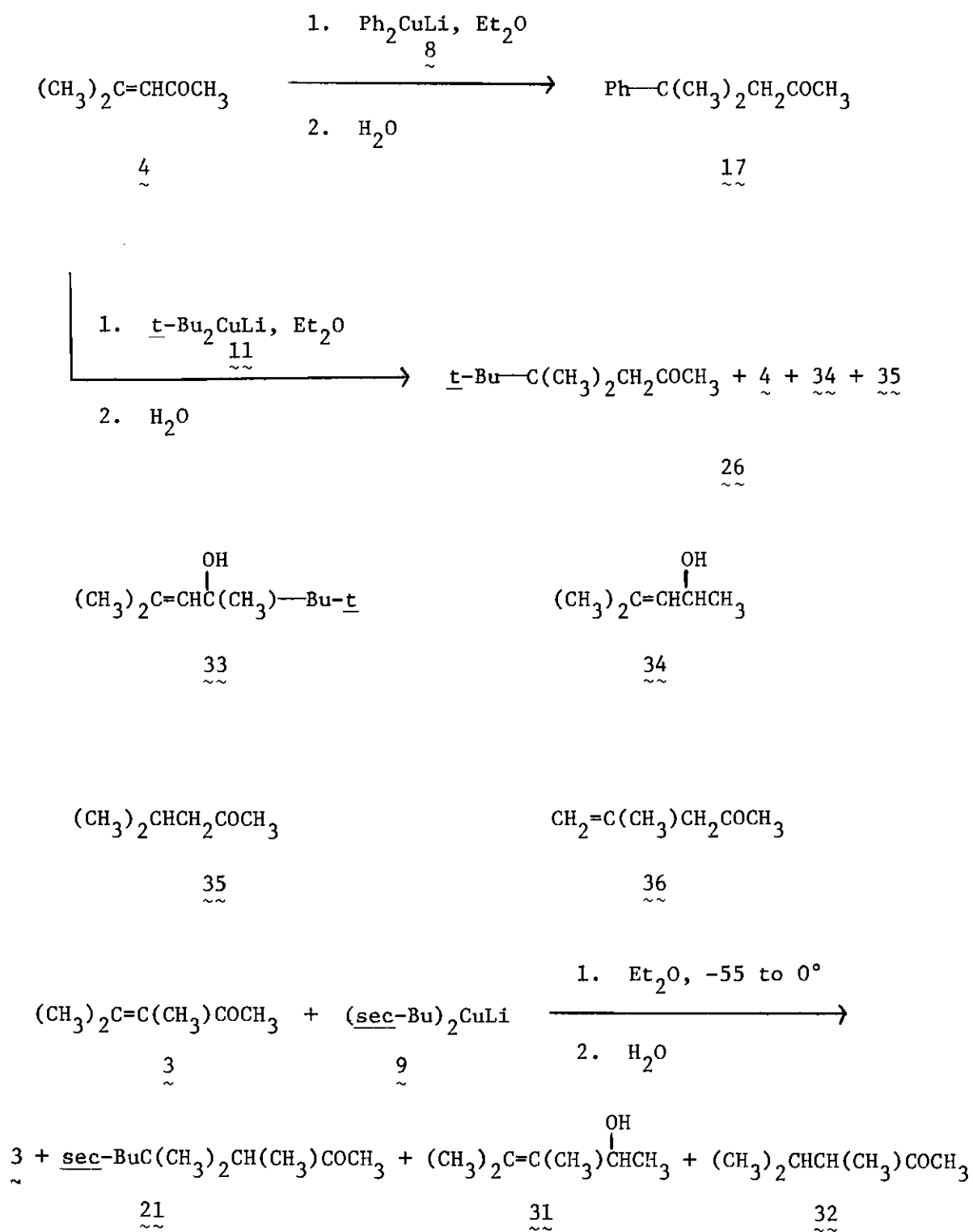
$R_2CuLi$ (solvent)	Reaction temperature, °C	Reaction products (% yield)		
		trans- $CH_3CH=CHCOCH_3$ 5 ( $E_{red}$ -2.08V)	$(CH_3)_2C=CHCOCH_3$ 4 ( $E_{red}$ -2.21V)	$(CH_3)_2C=C(CH_3)COCH_3$ 3 ( $E_{red}$ -2.35V)
$(n-Bu)_2CuLi$ 6 ( $Et_2O$ - $Me_2S$ -hexane, 1:3:3 v/v/v)	-20 to -30°	--	n-BuC(CH <sub>3</sub> ) <sub>2</sub> CH <sub>2</sub> COCH <sub>3</sub> 13 (83%)	n-BuC(CH <sub>3</sub> ) <sub>2</sub> CH(CH <sub>3</sub> )COCH <sub>3</sub> 14 (74%) + 3 (5%)
$(CH_2=CH)_2CuLi$ 7 ( $Et_2O$ - $Me_2S$ -THF, 1:1:1 v/v/v)	-20 to -35°	--	$CH_2=CHC(CH_3)_2CH_2COCH_3$ 15 (72%) <sup>a</sup>	$CH_2=CHC(CH_3)_2CH(CH_3)COCH_3$ 16 (55%) + 3 (17%) <sup>b</sup>
$Ph_2CuLi$ 8 ( $Me_2S$ - $Et_2O$ , 1:3 v/v)	10-27°	--	PhC(CH <sub>3</sub> ) <sub>2</sub> CH <sub>2</sub> COCH <sub>3</sub> 17 (77%)	PhC(CH <sub>3</sub> ) <sub>2</sub> CH(CH <sub>3</sub> )COCH <sub>3</sub> 18 (48%) + 3 (43%)
(sec-Bu) <sub>2</sub> CuLi 9 $Et_2O$ - $Me_2S$ -cyclohexane, (1:1:2 v/v/v)	-50 to -55°	sec-BuC(CH <sub>3</sub> )CH <sub>2</sub> COCH <sub>3</sub> 19 (87%)	sec-BuC(CH <sub>3</sub> ) <sub>2</sub> CH <sub>2</sub> COCH <sub>3</sub> 20 (77%)	sec-BuC(CH <sub>3</sub> ) <sub>2</sub> CH(CH <sub>3</sub> )COCH <sub>3</sub> 21 (17-43%) + 3 (19-45%)
$Me_2CuLi$ 10 ( $Et_2O$ )	10-30°	$(CH_3)_2CHCH_2COCH_3$ 22 (94%) <sup>c</sup>	$(CH_3)_3CCH_2COCH_3$ 23 (93%) <sup>d</sup>	$(CH_3)_3CCH(CH_3)COCH_3$ 24 (21%) + 3 (72%) <sup>e</sup>
(t-Bu) <sub>2</sub> CuLi 11 ( $Et_2O$ - $Me_2S$ -pentane, 1:1:1 v/v/v)	-55 to -65°	t-BuC(CH <sub>3</sub> )CH <sub>2</sub> COCH <sub>3</sub> 25 (74%)	t-BuC(CH <sub>3</sub> ) <sub>2</sub> CH <sub>2</sub> COCH <sub>3</sub> 26 (4%) + 4 (59-62%)	--
$(CH_2=CH)_2CuLi$ 12 ( $Et_2O$ )	-30 to -70°	$CH_2=CHCH_2CH(CH_3)CH_2-$ COCH <sub>3</sub> 27 (10-16%) + 5 (48-53%) + 28 (12-18%)	$CH_2=CHCH_2C(CH_3)_2CH_2-$ COCH <sub>3</sub> 29 (1%) + 4 (6%) + 30 (71%)	--

<sup>a</sup> This experiment is reported in Ref. 1f; <sup>b</sup> This experiment is described in Ref. 1b; <sup>c</sup> This experiment is described in H. O. House, W. L. Respess, and G. M. Whitesides, J. Org. Chem., 31, 3128 (1966); <sup>d</sup> This experiment is described in Ref. 1g; <sup>e</sup> This experiment is reported in Refs. 1b and 1g; the range of product compositions were 15-30% of 24 and 70-85% of 3.

Me(CH<sub>2</sub>=CH)CuLi derived from them] were allowed to compete for a limited amount of some conjugated substrate, the observed orders of reactivity were: CH<sub>2</sub>=CH > Me for additions of Me(CH<sub>2</sub>=CH)CuLi to several enones,<sup>1b,5</sup> n-Bu > sec-Bu > t-Bu > Ph for additions of R'RCuLi to CH<sub>2</sub>=CHCOCH<sub>3</sub>,<sup>6</sup> and t-Bu > i-Pr > n-Bu > Ph > Me for additions of R'RCuLi to CH<sub>2</sub>=C=CHP(O)Ph<sub>2</sub>.<sup>7</sup> Among these various reactivity orders, the order reported for additions to the allenic phosphine oxide<sup>7</sup> is rather different than all of the other studies. The remaining reactivity orders for additions to enones are consistent except for the position of the Ph<sub>2</sub>CuLi reagent. Our studies clearly indicate that Ph<sub>2</sub>CuLi will add conjugately to an enone 4 that gave only a very low yield (4%) of a conjugate adduct 26 with (t-Bu)<sub>2</sub>CuLi whereas in the earlier study of the addition of the mixed reagent Ph(t-Bu)CuLi to CH<sub>2</sub>=CHCOCH<sub>3</sub>, transfer of a t-Bu group was favored over transfer of a Ph group.<sup>6</sup> To explore the possibility that the presumed mixed cuprate Ph(t-Bu)CuLi might behave differently from the separate cuprate reagents 8 and 11, the enone 4 (Scheme I) was allowed to react with an excess of an equimolar mixture of cuprates 8 and 11. As our previous data would suggest, the major product formed in this reaction was the ketone 17 (98% of the conjugate addition product) formed by conjugate addition of a phenyl group. We therefore conclude that the order of reactivity is: Ph > t-Bu.

In the reaction of (sec-Bu)<sub>2</sub>CuLi with the difficultly reduced enone 3, the yields of recovered enone 3 and adduct 21 varied in a capricious manner. This reaction also yielded two by-products 31 and 32 formed by 1,2- or 1,4-reduction of the starting enone 3. Similar

## Scheme I



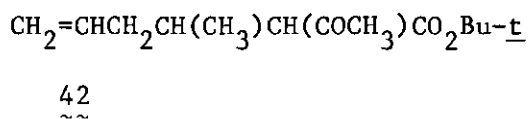
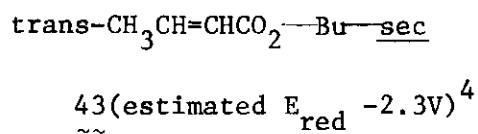
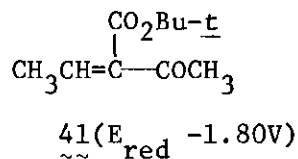
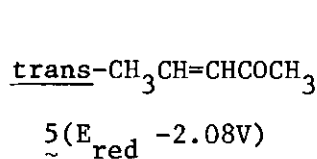
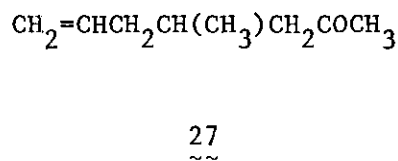
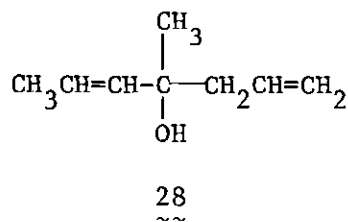
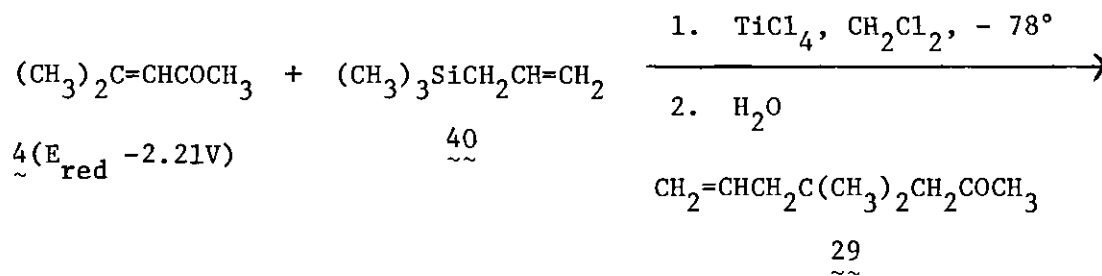
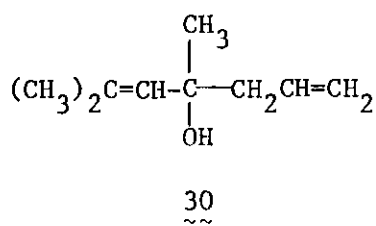
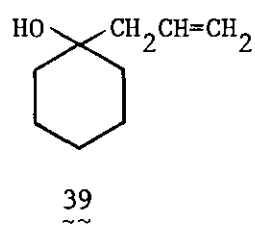
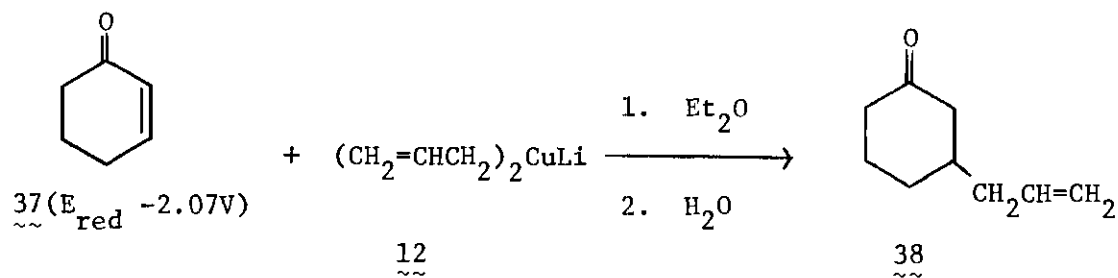
reduction products, the alcohol 34 and the ketone 35, were also observed as by-products in the sluggish reaction of the enone 4 with t-Bu<sub>2</sub>CuLi. We suspect that these by-products are formed by a competing reduction of the enone 3 or 4 by some copper hydride species of the type R(H)CuLi.<sup>8a-d,f</sup> It is not clear whether such a reagent is being formed by decomposition of (sec-Bu)<sub>2</sub>CuLi or t-Bu<sub>2</sub>CuLi, from prior partial decomposition of sec-BuLi or t-BuLi to form some LiH in the commercial lithium reagent, or from both sources. In any case this reduction side reaction was a problem only with the relatively slow reactions involving difficultly reduced enones and cuprates with secondary or tertiary alkyl substituents. The thermal decomposition of tertiary alkyl and allyl reagents, t-Bu<sub>2</sub>CuLi (11) and (allyl)<sub>2</sub>CuLi (12), appeared to be particularly sensitive to the presence of impurities [presumably Cu(II) derivatives] in the Cu(I) salt used to prepare the cuprate suggesting that autocatalytic decomposition<sup>8e</sup> of these reagents is especially favorable. Thus the t-Bu<sub>2</sub>CuLi (11) generated from freshly prepared (or freshly recrystallized) Me<sub>2</sub>SCuBr was obtained at -60° to -70° as a pale orange solution that reacted with the enone 4 to form, after hydrolysis, a mixture of the starting enone 4 and the conjugate adduct 26. However, when the cuprate 11 was prepared from samples of Me<sub>2</sub>SCuBr that had been stored for some time before use, partial decomposition of the cuprate 11 was evident (brown-black precipitate) even at -70° and a substantial amount (20% or more) of the 1,2-adduct 33 was formed upon addition of the enone 4. Thus decomposition of the cuprate 11 is apparently accompanied by the liberation of some



$t$ -BuLi that reacts with the enone to give a 1,2-adduct.

Our study of the allyl cuprate reagent 12 (Scheme II) represents an extension of earlier observations that although adding a CuCl catalyst failed to promote the conjugate addition of an allyl Grignard reagent to cyclohexenone 37 at 25°, <sup>9a</sup> this conjugate addition was successful when the enone 37 was treated with an Et<sub>2</sub>O solution of the allyl cuprate 12 at -70°. <sup>9b</sup> In retrospect, the early Cu-catalyzed Grignard reaction <sup>9a</sup> performed at 25°, could not have succeeded because the allyl copper reagents undergo rapid thermal decomposition at temperatures above -30°. More recently, the related cuprate reagent, [CH<sub>2</sub>=C(CH<sub>3</sub>)CH<sub>2</sub>]<sub>2</sub>CuLi, was also added to the enone 37 at -78° to form a derivative of the conjugate adduct in 86% yield <sup>10a</sup> and the allyl cuprate 12 was added to cyclopentenone (E<sub>red</sub> -2.16V) <sup>3</sup> to form the conjugate adduct in 95% yield. <sup>10b</sup> In the present study, repetition of the reaction of the enone 37 with the allyl cuprate reagent 12 again formed the conjugate adduct 38 in 91% yield with little or no by-product alcohol 39 provided that sufficient care was taken in purification of the reagents Me<sub>2</sub>SCuBr and CH<sub>2</sub>=CHCH<sub>2</sub>Li (from CH<sub>2</sub>=CHCH<sub>2</sub>OPh) <sup>11b</sup> and in controlling the reaction temperature. With the more difficultly reduced enone 4, the conjugate adduct 29 was obtained in only 1% yield and the alcohol 30 was the major product. The acyclic enone 5, with an E<sub>red</sub> value comparable to cyclohexenone (37), yielded a mixture of 1,4-adduct 27 (10-16%), 1,2-adduct 28 (12-18%), and recovered enone 5 (48-53%, presumably from initial metal enolate formation). In the latter

Scheme II



case, the proportions of products 5, 27, and 28 were comparable in reactions where the  $\text{CH}_2=\text{CHCH}_2\text{Li}$  used for the cuprate 12 was prepared either from  $\text{PhLi}$  and  $(\text{CH}_2=\text{CHCH}_2)_4\text{Sn}$ <sup>11a</sup> or from  $\text{Li}$  and  $\text{PhOCH}_2\text{CH}=\text{CH}_2$ <sup>11b</sup> (solution contains equimolar amounts of  $\text{PhOLi}$  and  $\text{CH}_2=\text{CHCH}_2\text{Li}$ ).

However, one difference dependent on the source of the  $\text{CH}_2=\text{CHCH}_2\text{Li}$  was observed. The red precipitate, previously suggested<sup>9b,10</sup> to be allylcopper, that resulted either when the allylcuprate solution was treated with a reactive enone or when the  $\text{Cu(I)}$  salt was treated with only 1 mol equiv of  $\text{CH}_2=\text{CHCH}_2\text{Li}$  was observed only with the  $\text{CH}_2=\text{CHCH}_2\text{Li}$  preparation that contained an equimolar amount of  $\text{PhOLi}$ . In reactions utilizing alkoxide-free  $\text{CH}_2=\text{CHCH}_2\text{Li}$  [from  $(\text{CH}=\text{CHCH}_2)_4\text{Sn}$ ], the above circumstances led to the formation of red-orange solutions but no red precipitate. These observations suggest that the above red precipitate may be some mixed cuprate cluster such as  $(\text{allyl})(\text{PhO})\text{CuLi}$ .

We also examined the reaction of the enone 5 with  $\text{CH}_2=\text{CHCH}_2\text{MgBr}$  at  $-40$  to  $-50^\circ$  in the presence of 27 mol % of  $\text{Me}_2\text{SCuBr}$ . The yield of 1,4-adduct 27 (13-20%) was similar to that obtained with the allylcuprate 12, but, as might be expected, the yield of alcohol 28 (53-60%) was higher and the amount of recovered enone 5 (4-8%) was lower. In the absence of a  $\text{Cu(I)}$  catalyst, each of the enones 4, 5, and 37 reacted with  $\text{CH}_2=\text{CHCH}_2\text{MgBr}$  to give a good yield of 1,2-adduct 28,<sup>12</sup> 30, or 39. When the more easily reduced derivative 41 of enone 5 was allowed to react at  $-70^\circ$  with  $\text{CH}_2=\text{CHCH}_2\text{MgBr}$  in the presence of 27 mol % of  $\text{Me}_2\text{SCuBr}$ , the corresponding conjugate adduct 42 was isolated in 75% yield.<sup>13</sup>

The foregoing observations suggest that the use of the cuprate reagent 12 or a Cu-catalyzed Grignard reaction to effect the conjugate addition of an allyl group to an enone is likely to be generally useful only with easily reduced enones ( $E_{\text{red}}$  less negative than  $-2.0\text{V}$ ). One apparent exception is the reported<sup>14</sup> conjugate addition of the allyl cuprate 12 to the ester 43 at  $-10$  to  $-15^\circ$  in an  $\text{Et}_2\text{O}$ -THF mixture. With simple enones (typical  $E_{\text{red}}$   $-2.1$  to  $-2.3\text{V}$ ) the alternative procedure of Hosomi and Sakurai<sup>15</sup> involving reaction of the enone with the allylsilane 40 in the presence of  $\text{TiCl}_4$  would seem to be clearly preferable for effecting the conjugate addition of an allyl group.

## Experimental Section<sup>16</sup>

### Preparation of Reagents

All solvents were purified by distillation from  $\text{LiAlH}_4$  immediately before use. Recrystallized samples of  $\text{Me}_2\text{SCuBr}$ <sup>1b</sup> were used to prepare all organocopper(I) derivatives. The  $\text{Me}_2\text{S}$  was purified by distillation from  $\text{LiAlH}_4$ , b.p.  $36-38^\circ$ . Pure samples of enones 5<sup>17</sup> and 3<sup>1b</sup> were obtained as previously described and a pure sample of enone 4 was obtained by fractional distillation<sup>18</sup> of commercial mesityl oxide, b.p.  $127-128^\circ$ ,  $n_{\text{D}}^{25}$   $1.4430$  (lit.<sup>18</sup> b.p.  $129.8^\circ$ ,  $n_{\text{D}}^{20}$   $1.44575$ ). Solutions of  $\text{PhLi}$ , obtained by reaction of  $\text{PhBr}$  with  $\text{Li}$  wire in  $\text{Et}_2\text{O}$ , were standardized by a double titration procedure<sup>19</sup> in which aliquots of the reagent, both before and after reaction with  $\text{BrCH}_2\text{CH}_2\text{Br}$ , were titrated with standard aqueous acid. The same standardization procedure<sup>19</sup> was used for commercial

solutions of n-BuLi (Foote Mineral Co.) in hexane, t-BuLi (Lithium Corporation of America) in pentane, and sec-BuLi (Foote Mineral Co.) in cyclohexane. Ethereal solutions of allylmagnesium bromide, prepared in the usual way,<sup>20</sup> were standardized by titration with sec-BuOH employing 2,2'-bipyridyl as the indicator.<sup>22</sup> Ethereal solutions of allyllithium, containing an equivalent amount of PhOLi, were prepared by a modification of a previously described procedure<sup>11b</sup> in which  $\text{PhOCH}_2\text{CH}=\text{CH}_2$  was allowed to react with Li in  $\text{Et}_2\text{O}$  solution. Alkoxide-free ethereal solutions of allyllithium were prepared by the previously described<sup>11a</sup> reaction of  $(\text{CH}_2=\text{CHCH}_2)_4\text{Sn}$  with ethereal PhLi. In each case the amounts of allyllithium and residual base in the solutions were determined by the double titration procedure.<sup>19</sup>

Freshly distilled commercial samples of enone 37 were used for electrochemical measurements employing previously described procedures.<sup>13,21</sup> Solutions in anhydrous DMF containing 0.5M n-Bu<sub>4</sub>NBF<sub>4</sub> and  $1.3\text{--}4.8 \times 10^{-3}\text{M}$  enone 37 exhibited a polarographic  $E_{1/2}$  value of -2.07V vs SCE ( $n=0.9$ ,  $i_d = 7 - 19 \mu\text{A}$ ).

#### Reactions of Ph<sub>2</sub>CuLi

A. With Enone 4. To a cold ( $10^\circ$ ) solution of 3.46 g (16.9 mmol) of Me<sub>2</sub>SCuBr in 15 ml of Me<sub>2</sub>S was added, dropwise with stirring and cooling during 20 min, 35.7 ml of an  $\text{Et}_2\text{O}$  solution containing 33.8 mmol of PhLi. To the resulting cold ( $10^\circ$ ) green solution was added 1.10 g (11.3 mmol) of enone 4. The resulting mixture, which warmed to  $34^\circ$  and slowly became a dark green-brown color, was stirred for 1 hr at  $27^\circ$  and the mixture was then partitioned between  $\text{Et}_2\text{O}$  and

an aqueous solution (pH 8) of  $\text{NH}_3$  and  $\text{NH}_4\text{Cl}$ . The organic layer was washed successively with aqueous  $\text{NH}_3$ , aqueous  $\text{NaCl}$ , and  $\text{H}_2\text{O}$  and then dried and concentrated to leave 2.16 g of crude liquid product. An aliquot was mixed with an internal standard ( $n\text{-C}_{16}\text{H}_{34}$ ) and subjected to glpc analysis (Carbowax 20M on Chromosorb P, apparatus calibrated with known mixtures of authentic samples); the product contained  $n\text{-C}_{16}\text{H}_{34}$  (ret. time 6.3 min), ketone 17 (77% yield, 19.0 min), and Ph-Ph (26.0 min). In three comparable reactions, the yields of ketone 17 were 76, 77, and 87%. A collected (glpc) sample of Ph-Ph was identified with an authentic sample by comparison of ir and mass spectra and glpc retention times. A collected (glpc) sample of the ketone 17 was obtained as a colorless liquid,  $n_{\text{D}}^{25} 1.5118$  [lit. b.p.  $61\text{--}62^\circ$  (1 mm),  $^{23a} 134^\circ$  (22 mm),  $^{23b} n_{\text{D}}^{20} 1.5115^{23a}$ ]; ir ( $\text{CCl}_4$ ),  $1725$  and  $1708\text{ cm}^{-1}$  ( $\text{C}=\text{O}$ ); nmr ( $\text{CCl}_4$ ),  $\delta 7.0\text{--}7.5$  (5H, m, aryl CH),  $2.58$  (2H, s,  $\text{CH}_2\text{CO}$ ),  $1.63$  (3H, s,  $\text{CH}_3\text{CO}$ ), and  $1.33$  (6H, s,  $\text{CH}_3$ ); uv (95% EtOH), series of weak maxima ( $\epsilon 60\text{--}243$ ) in the region  $239\text{--}278.5\text{ m}\mu$ ; mass spectrum,  $m/e$  (rel. intensity),  $176$  ( $\text{M}^+$ , 24),  $120$  (20),  $119$  (100),  $118$  (38),  $91$  (63), and  $43$  (58).

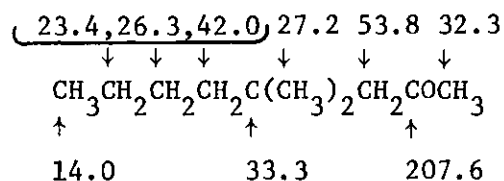
B. With Enone 3. To a solution (at  $20^\circ$ ) of  $\text{Ph}_2\text{CuLi}$ , prepared from 2.303 g (11.2 mmol) of  $\text{Me}_2\text{SCuBr}$  in 7 ml of  $\text{Me}_2\text{S}$  and 28 ml of  $\text{Et}_2\text{O}$  and 28 ml of an  $\text{Et}_2\text{O}$  solution containing 22.4 mmol of  $\text{PhLi}$ , was added, dropwise and with stirring, a solution of 896 mg (8.0 mmol) of the enone 3 in 12 ml of  $\text{Et}_2\text{O}$ . The reaction mixture, a green solution containing some white solid, was stirred at  $27^\circ$  for 1 hr and then subjected to the usual isolation procedure. An aliquot of the crude liquid product (1.74 g) was mixed with a known

amount of internal standard ( $n\text{-C}_8\text{H}_{17}\text{Ph}$ ) for glpc analysis (Carbowax 20M on Chromosorb P). The product contained (glpc) the enone 3 (retention time 10.2 min, 43% recovery),  $n\text{-C}_8\text{H}_{17}\text{Ph}$  (34.5 min), the ketone 18 (44.3 min, 48% yield), and Ph-Ph (47.9 min). Collected (glpc) samples of Ph-Ph and the enone 3 were identified with authentic samples by comparison of glpc retention times and ir and mass spectra. A collected (glpc) sample of the ketone 18 was obtained as a colorless liquid,  $n_{\text{D}}^{25}$  1.4468 [lit. bp 72-75° (0.15 mm), <sup>24a</sup> 129-130° (5 mm), <sup>24b</sup> 138.5° (18 mm), <sup>24c</sup>  $n_{\text{D}}^{25}$  1.4604, <sup>24b</sup> 1.5093<sup>24c</sup>]; ir ( $\text{CCl}_4$ ), 1711  $\text{cm}^{-1}$  (C=O); nmr ( $\text{CCl}_4$ ),  $\delta$  7.1 - 7.5 (5H, m, aryl CH), 2.91 (1H, q,  $J = 7.5$  Hz, CHCO), 1.68 (3H, s,  $\text{CH}_3\text{CO}$ ), 1.35 (6H, s,  $\text{CH}_3$ ), and 0.95 (3H, d,  $J = 7.5$  Hz,  $\text{CH}_3$ ); mass spectrum,  $m/e$  (rel. intensity), 190 ( $\text{M}^+$ , 5), 120 (11), 119 (100), 91 (37), 43 (30), and 41 (18); uv (95% EtOH), series of weak maxima ( $\epsilon$  174 - 248) in the region 246-264 m $\mu$  with an additional maximum at 289 m $\mu$  ( $\epsilon$  56).

#### Reaction of $n\text{-Bu}_2\text{CuLi}$

A. With Enone 4. To a cold (-20 to -30°) solution of  $n\text{-Bu}_2\text{CuLi}$ , from 14.35 g (70 mmol) of  $\text{Me}_2\text{SCuBr}$ , 75 ml of  $\text{Me}_2\text{S}$ , and 77.5 ml of a hexane solution containing 140 mmol of  $n\text{-BuLi}$ , was added, dropwise with stirring and cooling, a solution of 4.9 g (50 mmol) of the enone 4 in 20 ml of  $\text{Et}_2\text{O}$ . The resulting dark green-brown mixture was stirred at -20 to -30° for 20 min and then allowed to warm to 27° with stirring during 15 min. This warming was accompanied by thermal decomposition of the excess cuprate with separation of  $\text{Cu}^0$  as a black precipitate.

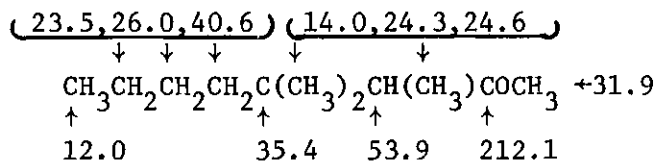
The reaction mixture was partitioned between Et<sub>2</sub>O and an aqueous solution (pH 8) of NH<sub>4</sub>Cl and NH<sub>3</sub>. The organic phase was filtered, washed successively with aqueous NH<sub>3</sub>, and with aqueous NaCl, and then dried and concentrated by fractional distillation. The residual yellow liquid (8.046 g) contained (glpc, Carbowax 20M on Chromosorb P) the ketone 13 (ret. time 11.7 min) accompanied by two minor unidentified impurities (4.5 and 5.3 min). A 7.060-g aliquot of the product was fractionally distilled to separate 5.670 g (83%) of the ketone 13 as a colorless liquid, bp 93-95° (30 mm),  $n_D^{25}$  1.4223. A collected (glpc) sample of the pure ketone 13 was obtained as a colorless liquid,  $n_D^{25}$  1.4240 [lit.<sup>25</sup> bp 62-64° (7 mm),  $n_D^{20}$  1.4250]; ir (CCl<sub>4</sub>), 1716 cm<sup>-1</sup> (C=O); uv max (95% EtOH), 284.5 mμ (ε 21); nmr (CCl<sub>4</sub>), δ 2.25 (2H, s, CH<sub>2</sub>CO), 2.04 (3H, s, CH<sub>3</sub>CO), and 0.8 - 1.5 (15H, m, aliphatic CH including a CH<sub>3</sub> singlet at 0.97); mass spectrum, m/e (rel. intensity), 156 (M<sup>+</sup>, <1), 98 (35), 69 (30), 58 (14), 57 (36), 56 (22), 43 (100), and 41 (16). The natural abundance <sup>13</sup>C nmr spectrum of the ketone 13 (CDCl<sub>3</sub>) is summarized in the following formula; the indicated assignments are consistent with off-resonance decoupling measurements.



B. With Enone 3. To a cold (-25°) solution of n-Bu<sub>2</sub>CuLi, from 2.173 g (10.6 mmol) of Me<sub>2</sub>SCuBr in 13 ml of Me<sub>2</sub>S and 13.9 ml



of a hexane solution containing 21.2 mmol of n-BuLi, was added, dropwise with stirring and cooling, a solution of 846 mg (7.55 mmol) of the enone 3 in 4 ml of Et<sub>2</sub>O. After the resulting dark-colored solution had been stirred at -25° for 15 min, it was warmed to 27° during 15 min and then subjected to the previously described isolation procedure. After an aliquot of the crude liquid product (1.94 g) had been mixed with a known weight of internal standard (n-BuPh), analysis (glpc, Carbowax 20M on Chromosorb P) indicated the presence of the starting enone 3 (retention time 8.3 min, ca. 5% recovery), n-BuPh (12.0 min), and the adduct 14 (18.9 min, 74% yield). A collected (glpc) sample of the ketone 14 was obtained as a colorless liquid, n<sub>D</sub><sup>25</sup> 1.4336; ir (CCl<sub>4</sub>), 1711 cm<sup>-1</sup> (C=O); uv max (95% EtOH), 285.5 mμ (ε 17); nmr (CCl<sub>4</sub>), δ 2.49 (1H, q, J = 7 Hz, CHCO), 2.08 (3H, s, COCH<sub>3</sub>), and 0.8 - 1.5 (18H, m, aliphatic CH including a CH<sub>3</sub> singlet at 0.90); mass spectrum, m/e (rel. intensity), 170 (M<sup>+</sup>, <1), 98 (19), 72 (100), 71 (15), 57 (50), and 43 (61). The natural abundance <sup>13</sup>C nmr spectrum of the ketone 14 (CDCl<sub>3</sub>) is summarized in the following formula; the indicated assignments are consistent with off-resonance decoupling measurements.



Anal. Calcd for C<sub>11</sub>H<sub>22</sub>O: C, 77.58; H, 13.02. Found:

C, 77.47; H, 13.04.

Reaction of  $t\text{-Bu}_2\text{CuLi}$

A. With Enone 4. To a cold ( $-72^\circ$ ) solution of 11.73 g (57.1 mmol) of freshly recrystallized  $\text{Me}_2\text{SCuBr}$  in 50 ml of  $\text{Et}_2\text{O}$  and 62 ml of  $\text{Me}_2\text{S}$  was added, dropwise with stirring and cooling during 45 min, 68.3 ml of a pentane solution containing 114 mmol of  $t\text{-BuLi}$ . The temperature was maintained at  $-72^\circ$  to  $-65^\circ$  during this addition. The yellow to orange precipitate that separated during the initial phase of the addition redissolved as the remainder of the  $t\text{-BuLi}$  was added to give an orange solution of  $t\text{-Bu}_2\text{CuLi}$ . A solution of 3.83 g (39.1 mmol) of the enone 4 in 10 ml of  $\text{Et}_2\text{O}$  was added, dropwise and with stirring during 10 min, to the cold solution of  $t\text{-Bu}_2\text{CuLi}$  while the mixture was maintained at  $-65^\circ$ . During the addition of the enone 4 the solution turned red and a red precipitate separated. The resulting mixture was stirred at  $-60^\circ$  for 45 min and then allowed to warm to  $0^\circ$  over a period of 20 min. During this warming thermal decomposition (separation of brown-black solid) was evident as the temperature rose above  $-25^\circ$ . The reaction mixture was partitioned between  $\text{Et}_2\text{O}$  and an aqueous solution of  $\text{NH}_4\text{Cl}$  and  $\text{NH}_3$ . The organic phase was washed with aqueous  $\text{NaCl}$ , dried, concentrated, and mixed with a known weight of  $n\text{-C}_{14}\text{H}_{30}$  (an internal standard). Analysis [glpc,  $74^\circ$  with FFAP (a modified Carbowax) on Chromosorb P, apparatus calibrated with known mixtures] indicated the presence of the starting enone 4 (ret. time 2.9 min, 51% recovery), the isomerized

enone 36 (2.2 min, 11% yield), the alcohol 34 (5.3 min, 10% yield), the ketone 26 (11.6 min, 3.5% yield), and  $n\text{-C}_{14}\text{H}_{30}$  (26.2 min). A peak corresponding in retention time (1.8 min) to ketone 35, the conjugate reduction product of enone 4, was also observed. Under the conditions used for this analysis the subsequently described alcohol 33 exhibited a glpc peak at 10.1 min. In another comparable experiment employing 1,3,5-(*i*-Pr)<sub>3</sub>C<sub>6</sub>H<sub>3</sub> (ret. time 31.0 min) as the internal standard, the yields and retention times of the products were: 4, 57% (3.0 min); 36, 1.9% (2.3 min); 34, 4.5% (5.6 min); and 26, 4.7% (12.7 min). Collected (glpc) samples of ketones 4 and 36 and alcohol 34 were identified with authentic samples by comparison of glpc retention times and ir and mass spectra. A collected (glpc) sample of the ketone 26 was obtained as a colorless liquid,  $n_{\text{D}}^{25}$  1.4416 [lit.<sup>26</sup> bp 196.1°,  $n_{\text{D}}^{20}$  1.4420]; ir (CCl<sub>4</sub>), 1715 (shoulder) and 1708 cm<sup>-1</sup> (C=O); nmr (CCl<sub>4</sub>),  $\delta$  2.29 (2H, s, CH<sub>2</sub>CO), 2.05 (3H, s, CH<sub>3</sub>CO), 0.97 (6H, s, CH<sub>3</sub>), and 0.87 (9H, s, *t*-Bu); mass spectrum, *m/e* (rel. intensity), 141 (9), 123 (9), 101 (24), 100 (57), 99 (26), 98 (26), 85 (58), 83 (71), 57 (69), 55 (36), 43 (100), 41 (58), and 39 (31).

In an experiment where the cuprate reagent was prepared at -57 to -65° from 14.65 g (71.5 mmol) of Me<sub>2</sub>SCuBr (not freshly purified), 60 ml of Me<sub>2</sub>S, and 72.2 ml of a pentane solution containing 143 mmol of *t*-BuLi, at least partial decomposition of the cuprate occurred during its preparation. After the resulting cold (-65°) dark-colored mixture had been treated with a solution of 5.00 g (51.0 mmol) of the enone 4 in 20 ml of Et<sub>2</sub>O, the resulting mixture

was stirred at  $-60$  to  $-65^{\circ}$  for 20 min and then allowed to warm to room temperature with stirring during 15 min. After following the usual isolation procedure, the residual crude liquid product (3.63 g) contained (ir and nmr analysis) a mixture of the starting enone 4 and the alcohol 33 with little if any saturated ketone product. A 3.12 g-aliquot of this crude product was distilled in a short path still to separate 1.37 g (20%) of the pure alcohol 33 as a colorless liquid, bp  $30-31^{\circ}$  (0.4 mm),  $n_D^{25}$  1.4510 - 1.4512, that was identified with the subsequently described sample by comparison of ir and nmr spectra. A collected (glpc) sample of the starting enone 4 was identified with an authentic sample by comparison of glpc retention times and ir spectra.

To obtain an authentic sample of the alcohol 33, a solution of 153 mmol of t-BuLi in 135 ml of pentane was cooled to  $-72^{\circ}$  and then a solution of 7.497 g (76.5 mmol) of the ketone 4 in 25 ml of  $\text{Et}_2\text{O}$  was added, dropwise and with stirring while the temperature of the reaction mixture was maintained at  $-65$  to  $-72^{\circ}$ . After the resulting yellow mixture had been stirred at  $-72^{\circ}$  for 30 min, it was warmed to  $-30^{\circ}$  and siphoned into  $\text{H}_2\text{O}$ . This mixture was saturated with NaCl, and extracted with  $\text{Et}_2\text{O}$ . After the ethereal solution had been dried and concentrated, the residue, 11.89 g of liquid containing (ir and nmr analysis) mainly the alcohol 33, was fractionally distilled in apparatus that had been washed with aqueous  $\text{NH}_3$  and dried before use. The alcohol 33 was collected as 3.83 g (33%) of colorless liquid, bp  $28 - 33^{\circ}$  (0.42 mm),  $n_D^{25}$  1.4500 - 1.4508 [lit. bp  $180 - 185^{\circ}$ ,  $^{26}$   $46^{\circ}$  (4 mm),  $^{27a}$   $n_D^{20}$  1.4502 $^{27a}$ ]; ir

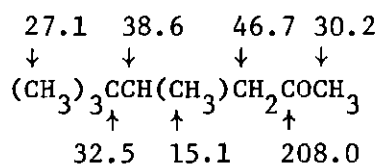
(CCl<sub>4</sub>), 3610, 3500 (OH), and 1665 cm<sup>-1</sup> (weak, C=C); nmr (CCl<sub>4</sub>),  $\delta$  5.1 - 5.4 (1H, m, vinyl CH), 1.87 (3H, d, J = 1.5 Hz, allylic CH<sub>3</sub>), 1.72 (3H, d, J = 1.5 Hz, allylic CH<sub>3</sub>), 1.23 (3H, s, CH<sub>3</sub>), and 0.92 (9H, s, *t*-Bu); mass spectrum, m/e (rel. intensity), 138 (13), 123 (84), 81 (85), 79 (20), 67 (34), 57 (59), 55 (42), 53 (30), 43 (55), 42 (100), and 39 (58).

Reduction of 1.02 g (10.4 mmol) of the enone 4 with 564 mg (14.9 mmol) of LiAlH<sub>4</sub> in 18 ml of Et<sub>2</sub>O followed by hydrolysis with a limited amount (2.2 ml) of aqueous NaOH and the usual isolation procedure yielded 635 mg (61%) of the alcohol 34 as a colorless liquid, bp 37 - 45° (10 mm),  $n_{D}^{25}$  1.4350 [lit.<sup>27b</sup> bp 63° (36 mm),  $n_{D}^{18}$  1.440]; ir (CCl<sub>4</sub>), 3608, 3420 (broad, OH) and 1674 cm<sup>-1</sup> (C=C); nmr (CCl<sub>4</sub>),  $\delta$  4.1 - 5.3 (2H, m, vinyl CH and CH-O), 3.13 (1H, broad, OH), 1.63 (6H, d, J = 1 Hz, allylic CH<sub>3</sub>), and 1.11 (3H, d, J = 6 Hz, CH<sub>3</sub>); mass spectrum, m/e (rel. intensity), 100 (M<sup>+</sup>, 7), 85 (100), 82 (20), 67 (73), 55 (21), 45 (25), 43 (57), 41(77), and 39 (36).

B. With Enone 5. To a cold (-55 to -60°) red-colored solution of *t*-Bu<sub>2</sub>CuLi, formed at -60 to -65° from 3.73 g (18.2 mmol) of Me<sub>2</sub>SCuBr in 15 ml of Me<sub>2</sub>S and 20.6 ml of a pentane solution containing 33.4 mmol of *t*-BuLi, was added, dropwise with stirring and cooling, a solution of 1.007 g (12.0 mmol) of the enone 5 in 6 ml of Et<sub>2</sub>O. After the reaction mixture had been stirred at -55° for 30 min, it was allowed to warm to 27° during 30 min and then subjected to the usual isolation procedure. An aliquot of the crude liquid product (1.72 g) was mixed with a known amount of

internal standard (durene) and analyzed by glpc (silicone QF<sub>1</sub> on Chromosorb P). The product contained (glpc) durene (retention time 12.9 min) and the ketone 25 (19.9 min, 74% yield) as well as two minor unidentified volatile by-products (3.9 and 10.8 min).

A collected (glpc) sample of the ketone 25 was obtained as a colorless liquid,  $n_D^{25}$  1.4227 [lit.<sup>28</sup> bp 162° (735 mm),  $n_D^{20}$  1.4275]; ir (CCl<sub>4</sub>), 1718 cm<sup>-1</sup> (C=O); uv max (95% EtOH), 277.5 mμ (ε 34); nmr (CCl<sub>4</sub>), δ 1.7 - 2.7 (6H, m, aliphatic CH including a CH<sub>3</sub>CO singlet at 2.05) and 0.7 - 0.95 (12H, *t*-Bu singlet at 0.85 partially resolved from a CH<sub>3</sub> doublet); mass spectrum, m/e (rel. intensity), 142 (M<sup>+</sup>, <1), 127 (7), 86 (32), 71 (36), 57 (65), 43 (100), and 41 (39). The natural abundance <sup>13</sup>C nmr spectrum (CDCl<sub>3</sub>) is summarized in the following formula; the indicated assignments are consistent with off-resonance decoupling measurements.



#### Reaction of the Enone 4 With a Mixture of *t*-Bu<sub>2</sub>CuLi and Ph<sub>2</sub>CuLi

A cooled (15°) solution of 2.02 g (9.82 mmol) of Me<sub>2</sub>SCuBr (recrystallized before use) in 8.5 ml of Et<sub>2</sub>O and 14.5 ml of Me<sub>2</sub>S was treated with 8.85 ml of an Et<sub>2</sub>O solution containing 9.82 mmol of PhLi (from PhBr and Li). The resulting greenish yellow slurry was cooled to -72° and 5.88 ml of a pentane solution containing 9.82 mmol of *t*-BuLi was added dropwise and with stirring while

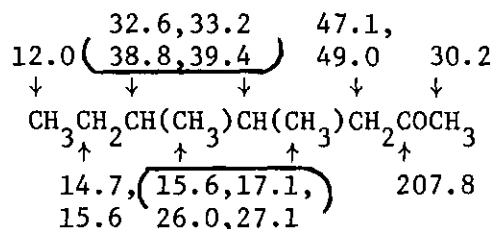
the temperature was maintained at  $-65$  to  $-72^{\circ}$ . After the resulting solution of the cuprates had been stirred at  $-70^{\circ}$  for 10 min a solution of 317 mg (3.24 mmol) of the enone 4, 91 mg of  $n\text{-C}_{16}\text{H}_{34}$  (internal standard), and 61 mg of 1,3,5- $(i\text{-Pr})_3\text{C}_6\text{H}_3$  (internal standard) in 2 ml of  $\text{Et}_2\text{O}$  was added dropwise and with stirring at  $-62$  to  $-68^{\circ}$ . During the addition of the enone a red precipitate  $[(t\text{-BuCu})_n]$  separated. The reaction mixture was stirred at  $-72^{\circ}$  for 1 hr and then was allowed to warm to  $25^{\circ}$  during 45 min. After the mixture had been quenched in an aqueous solution of  $\text{NH}_4\text{Cl}$  and  $\text{NH}_3$ , it was filtered to remove precipitated Cu and then extracted with  $\text{Et}_2\text{O}$ . The  $\text{Et}_2\text{O}$  solution was washed with aqueous NaCl, dried, and analyzed by glpc [FFAP (a modified Carbowax) on Chromosorb P, apparatus calibrated with known mixtures]. With the glpc column at  $74^{\circ}$ , the yields and retention times of the components were: enone 36, 0.4% yield (2.5 min); enone 4, 6.4% recovery (3.5 min); alcohol 34, 3.3% yield (5.7 min); alcohol 33, 0.7% yield (10.5 min); ketone 26, 1.3% yield (11.7 min); and 1,3,5- $(i\text{-Pr})_3\text{C}_6\text{H}_3$  (32.2 min). With the glpc column at  $141^{\circ}$  the yields and retention times of the components were:  $n\text{-C}_{16}\text{H}_{34}$  (7.9 min); ketone 17, 67% yield (16.7 min); and Ph-Ph (22.7 min). From a second comparable reaction the product yields were: 36, 3.1%; 4, 6.4%; 34, 7.9%; 26, 1.6%; and 17, 77%. A collected sample of the major product, ketone 17, was identified with an authentic sample by comparison of glpc retention times and ir spectra. Thus the ratio of conjugated addition products 26 (t-Bu addition) to 17 (Ph additon) was 2:98.

# Reactions of sec-Bu<sub>2</sub>CuLi

A. With Enone 5. To a cold (-72°) mixture of 3.80 g (18.5 mmol) of Me<sub>2</sub>SCuBr, 10 ml of Me<sub>2</sub>S, and 10 ml of Et<sub>2</sub>O was added, dropwise with stirring and cooling, 27.4 ml of a cyclohexane solution containing 36.9 mmol of sec-BuLi. After the resulting solution of sec-Bu<sub>2</sub>CuLi had been stirred for 5 min at -55°, a solution of 1.108 g (13.2 mmol) of the enone 5 in 4 ml of Et<sub>2</sub>O was added dropwise with stirring while the mixture was kept at -50 to -55°. The resulting reaction mixture was stirred at -50° for 20 min and then allowed to warm to 0° with stirring during 10 min. After the mixture had been partitioned between Et<sub>2</sub>O and an aqueous solution of NH<sub>3</sub> and NH<sub>4</sub>Cl, the organic phase was dried, concentrated, and mixed with a known weight of internal standard (tetralin). The crude product contained (glpc, Carbowax 20M on Chromosorb P, apparatus calibrated with known mixtures) the ketone 19 (ret. time 10.9 min, diastereoisomers not resolved, yield 87%), tetralin (32.1 min) and two minor unidentified alcohol (ir analysis) impurities (5.3 min and 21.0 min) but lacked a glpc peak for the starting enone 5 (4.5 min). A collected (glpc) sample of the ketone 19 was obtained as a colorless liquid, n<sub>D</sub><sup>25</sup> 1.4236 [lit.<sup>29</sup> bp 71 - 73° (15 min)]; ir (CCl<sub>4</sub>), 1720 cm<sup>-1</sup> (C=O); uv max (95% EtOH), 278 mμ (ε 25); nmr (CCl<sub>4</sub>), δ 1.6 - 2.8 (6H, m, aliphatic CH including a CH<sub>3</sub>CO singlet at 2.06) and 0.6 - 1.1 (12H, m, aliphatic CH); mass spectrum, m/e (rel. intensity), 142 (M<sup>+</sup>, <1), 85 (35), 84 (59), 69 (25), 58 (26), 57 (22), 43 (100), and 41 (22). The natural abundance <sup>13</sup>C nmr spectrum (CDCl<sub>3</sub>) of the ketone 19 is

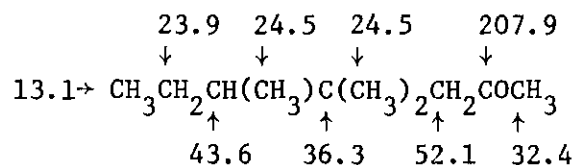


summarized in the following structure. Since two diastereoisomers are present in this sample, two chemical shift values are given for each carbon atom where the two diastereoisomers have different chemical shifts.



B. With Enone 4. To a cold ( $-50$  to  $-55^\circ$ ) solution of sec-Bu<sub>2</sub>CuLi, from 3.38 g (16.4 mmol) of Me<sub>2</sub>SCuBr, 10 ml of Me<sub>2</sub>S, 10 ml of Et<sub>2</sub>O, and 23.2 ml of a cyclohexane solution containing 31.3 mmol of sec-BuLi, was added, dropwise with stirring and cooling, a solution of 1.096 g (11.2 mmol) of the enone 4 in 4 ml of Et<sub>2</sub>O. After the reaction mixture had been stirred for 20 min at  $-50^\circ$  and for an additional 10 min while it was allowed to warm to  $0^\circ$ , the usual isolation procedure was followed and the crude neutral product was mixed with a known amount of internal standard (sec-Bu-Ph). The crude product contained (glpc, Carbowax 20 M on Chromosorb P, apparatus calibrated with known mixtures) sec-Bu-Ph (ret. time 10.9 min), the ketone 20 (18.3 min, yield 77%), and two minor unidentified impurities (5.6 min and 35.0 min). A collected (glpc) sample of the ketone 20 was obtained as a colorless liquid,  $n_D^{25}$  1.4330; ir (CCl<sub>4</sub>)  $1720\text{ cm}^{-1}$  (C=O); uv max (95% EtOH);  $284\text{ m}\mu$  ( $\epsilon$  25); nmr (CCl<sub>4</sub>),  $\delta$  2.36 (2H, s, CH<sub>2</sub>CO), 2.12 (3H, s,

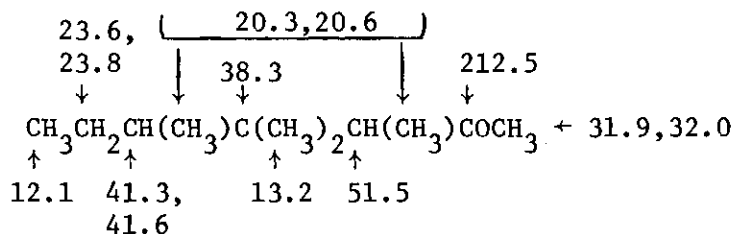
CH<sub>3</sub>CO), and 0.6 - 1.8 (15H, m, aliphatic CH including a CH<sub>3</sub> singlet at 0.96); mass spectrum m/e (rel. intensity), 141 (1), 99 (17), 98 (38), 83 (25), 57 (17), 43 (100), and 41 (12). The natural abundance <sup>13</sup>C nmr spectrum (CDCl<sub>3</sub>) of the ketone 20 is summarized in the following structure; the indicated assignments are consistent with off-resonance decoupling measurements.



Anal. Calcd for C<sub>10</sub>H<sub>20</sub>O: C, 76.86; H, 12.90. Found: C, 76.60; H, 12.89.

C. With Enone 3. To a cold (-68 to -72°) solution of sec-Bu<sub>2</sub>CuLi, from 6.80 g (33.1 mmol) of Me<sub>2</sub>SCuBr, 25 ml of Me<sub>2</sub>S, 25 ml of Et<sub>2</sub>O, and 45.3 ml of a cyclohexane solution containing 66.2 mmol of sec-BuLi, was added 2.523 g (22.5 mmol) of the enone 3 in 2 ml of Et<sub>2</sub>O. After the resulting mixture had been stirred at -55 to -60° for 30 min and at -45 to -60° for 90 min, it was warmed to 0° during 10 min and then subjected to the usual isolation procedure. After the crude liquid product had been mixed with an internal standard (1,3,5-triisopropylbenzene), analysis [glpc, FFAP (Regis Chemical Co.) on Chromosorb P] indicated the presence of the ketone 32 (ret. time 4.1 min, 5% yield), the starting enone 3 (9.6 min, 20% yield), the alcohol 31 (23.9 min, 13% yield), and the ketone 21 (35.6 min, the two diastereoisomers were not resolved,

19% yield), and 1,3,5-i-Pr<sub>3</sub>C<sub>6</sub>H<sub>3</sub> (59.5 min). From a number of comparable reactions, the following ranges of yields were observed for the various products: 32, 5-10%; 3, 19-45%; 31, 13-34%; 21, 17-43%. Collected (glpc) samples of products 3, 31, and 32 were identified with authentic samples by comparison of ir and mass spectra and glpc retention times. A collected (glpc) sample of the ketone 21 was obtained as a colorless liquid,  $n_D^{25}$  1.4430; ir (CCl<sub>4</sub>), 1713 cm<sup>-1</sup> (C=O); uv max (95% EtOH), 288 nm ( $\epsilon$  36); <sup>1</sup>H nmr (CCl<sub>4</sub>),  $\delta$  2.5 - 2.9 (1H, m, CHCO), 2.07 (3H, s, CH<sub>3</sub>CO), and 0.7 - 1.4 (18H, m, aliphatic CH); mass spectrum, m/e (rel. intensity), 137 (1), 113 (11), 99 (11), 98 (31), 83 (23), 72 (16), 57 (34), 55 (12), 43 (100), and 41 (14). The natural abundance <sup>13</sup>C nmr spectrum (CDCl<sub>3</sub>) of ketone 21 is summarized in the following structure; the indicated assignments are consistent with off-resonance decoupling measurements. Since the product is a mixture of two diastereoisomers, certain of the <sup>13</sup>C nmr signals appear as two peaks.



Anal. Calcd for C<sub>11</sub>H<sub>22</sub>O: C, 77.58; H, 13.02. Found C, 77.57; H, 13.02.

To obtain an authentic sample of the alcohol 31, 1.00 g

(8.93 mmol) of the enone 3 was reduced with 177 mg (4.65 mmol) of  $\text{LiAlH}_4$  in 8 ml of refluxing  $\text{Et}_2\text{O}$  for 30 min. After addition of 0.7 ml of  $\text{H}_2\text{O}$  and 0.2 ml of aqueous 15%  $\text{NaOH}$  to precipitate the metal salts, the  $\text{Et}_2\text{O}$  solution was dried, concentrated and distilled to separate the alcohol 31 as a colorless liquid, bp  $41\text{--}42^\circ$  (12 mm),  $n_D^{25}$  1.4508 [lit.<sup>30</sup> bp  $65\text{--}68^\circ$  (25 mm)]; ir ( $\text{CCl}_4$ ),  $3615$  and  $3470\text{ cm}^{-1}$  (OH); nmr ( $\text{CCl}_4$ ),  $\delta$  4.72 (1H, q,  $J = 6.5$  Hz, CH-O), 2.70 (1H, s, OH), 1.4 - 1.8 (9H, m, allylic  $\text{CH}_3$ ), and 1.10 (3H, d,  $J = 6.5$  Hz,  $\text{CH}_3$ ), mass spectrum, m/e (rel. intensity), 114 ( $\text{M}^+$ , 20), 99 (64), 96 (18), 81 (44), 79 (15), 55 (30), 53 (19), 45 (17), 43 (100), 41 (43), and 39 (25).

An authentic sample of the ketone 32 was obtained by hydrogenating a solution of 0.40 g (3.5 mmol) of the enone 3 in 8 ml of  $\text{EtOH}$  over 30 mg of a 5% Pd-on-C catalyst at  $25^\circ$  and 1 atm of  $\text{H}_2$ . After 8 hr the  $\text{H}_2$  uptake (3.9 mmol) ceased and the mixture was filtered and concentrated. A collected (glpc) sample of the ketone 32<sup>31</sup> was obtained as a colorless liquid,  $n_D^{25}$  1.4070 (lit. bp  $135\text{--}140^\circ$ , <sup>31a</sup>  $136\text{--}138^\circ$ <sup>31b</sup>); ir ( $\text{CCl}_4$ ),  $1713\text{ cm}^{-1}$  (C=O); nmr ( $\text{CCl}_4$ ),  $\delta$  1.7 - 2.3 (5H, m, aliphatic CH including a  $\text{CH}_3\text{CO}$  singlet at 2.04) and 0.7 - 1.3 (9H, m,  $\text{CH}_3$ ); mass spectrum, m/e (rel. intensity), 114 ( $\text{M}^+$ , 2), 72 (22), 71 (19), 55 (12), 43 (100), and 41 (20).

#### Reaction of $(\text{CH}_2=\text{CHCH}_2)_2\text{CuLi}$

A. With Enone 37. To a cold ( $-72^\circ$ ) partial solution of 545 mg (2.65 mmol) of freshly purified  $\text{Me}_2\text{SCuBr}$  in 4 ml of  $\text{Me}_2\text{S}$  and 4 ml of  $\text{Et}_2\text{O}$  was added, dropwise and with stirring, a solution

of 5.30 mmol of  $\text{CH}_2=\text{CHCH}_2\text{Li}$  (from  $\text{PhOCH}_2\text{CH}=\text{CH}_2$ ) in 6.3 ml of  $\text{Et}_2\text{O}$  while the temperature was maintained at  $-60$  to  $-68^\circ$ . As this addition proceeded the white precipitate ( $\text{Me}_2\text{SCuBr}$ ) was replaced by a red precipitate (presumably a derivative of allylcopper) and finally a clear red solution of  $(\text{CH}_2=\text{CHCH}_2)_2\text{CuLi}$  was obtained. To this solution was added, dropwise and with stirring, a solution of 126 mg (1.31 mmol) of the enone 37 and 94 mg of  $\text{Ph-C}_8\text{H}_{17}\text{-n}$  in 4 ml of  $\text{Et}_2\text{O}$ . The resulting mixture from which a red precipitate separated during the addition of the enone, was stirred at  $-72^\circ$  for 3 hr and then allowed to warm to  $27^\circ$  overnight. During the warming decomposition of the excess cuprate reagent was evident (separation of a fine black precipitate) as the temperature of the reaction mixture rose above  $-30^\circ$ . The final reaction mixture was added, dropwise and with stirring, to an aqueous solution of  $\text{NH}_4\text{Cl}$  and  $\text{NH}_4\text{OH}$  and the resulting mixture was extracted with  $\text{Et}_2\text{O}$ . After the ethereal solution had been washed successively with aqueous 10%  $\text{NaOH}$  (to remove  $\text{PhOH}$  from the  $\text{PhOCH}_2\text{CH}=\text{CH}_2$ ) and with aqueous  $\text{NaCl}$ , it was dried, concentrated, and analyzed [glpc, FFAP (regis Chemical Co.) on Chromosorb P, apparatus calibrated known mixtures]. The product contained the ketone 38 (ret. time 11.1 min, yield 91%),  $\text{Ph-C}_8\text{H}_{17}\text{-n}$  (22.0 min), and a minor unidentified impurity (3.4 min) but did not exhibit a glpc peak corresponding to the alcohol 39 (9.6 min).

A comparable reaction was run employing the cuprate, from 3.60 g (17.5 mmol) of  $\text{Me}_2\text{SCuBr}$ , 35 mmol of  $\text{CH}_2=\text{CHCH}_2\text{Li}$  (from  $\text{PhOCH}_2\text{CH}=\text{CH}_2$ ), 23 ml of  $\text{Me}_2\text{S}$ , and 38 ml of  $\text{Et}_2\text{O}$ , with a solution of

1.20 g (12.5 mmol) of the enone 37 in 5 ml of Et<sub>2</sub>O. After the mixture had been stirred at -72° for 1 hr and then warmed to 0° during 15 min, the previously described isolation procedure separated 1.50 g of the crude product as a yellow liquid. Short-path distillation of a 1.39-g aliquot of this product separated 910 mg (57%) of the ketone 38 as a colorless liquid,  $n_D^{25}$  1.4720 - 1.4721, that was identified with the previously described<sup>9b</sup> sample by comparison of ir, nmr, and mass spectra.

A solution of 5.00 g (52.1 mmol) of the enone 37 in 10 ml of Et<sub>2</sub>O was added, dropwise and with stirring during 20 min, to a solution containing 60 mmol of CH<sub>2</sub>=CHCH<sub>2</sub>MgBr in 68 ml of Et<sub>2</sub>O. After the resulting mixture had been stirred at 25° for 12 hr, it was poured into aqueous NH<sub>4</sub>Cl and extracted with Et<sub>2</sub>O. The organic layer was dried and concentrated to leave 6.74 g of the crude alcohol 39. Fractional distillation afforded 1.01 g of forerun, bp 35-40° (0.06 mm),  $n_D^{25}$  1.5154, and 3.58 g (50%) of the pure alcohol 39 as a colorless liquid, bp 40-42° (0.05 mm),  $n_D^{25}$  1.4932; ir (CCl<sub>4</sub>), 3620, 3480 (OH), 1640 (C=C), and 912 cm<sup>-1</sup> (CH=CH<sub>2</sub>); nmr (CCl<sub>4</sub>), δ 4.7 - 6.2 (5H, m, vinyl CH), 2.48 (1H, s, OH), and 1.0 - 2.3 (8H, m, CH<sub>2</sub>); mass spectrum, m/e (rel. intensity) 120 (6), 97 (100), 79 (32), 55 (37), 41 (33), and 39 (30).

Anal. Calcd for C<sub>9</sub>H<sub>14</sub>O: C, 78.21; H, 10.21. Found: C, 78.18; H, 10.24.

B. With Enone 4. To a cold (-65 to -72°) solution of (CH<sub>2</sub>=CHCH<sub>2</sub>)<sub>2</sub>CuLi, from 417 mg (2.03 mmol) of Me<sub>2</sub>SCuBr, 4.06 mmol of CH<sub>2</sub>=CHCH<sub>2</sub>Li (from PhOCH<sub>2</sub>CH=CH<sub>2</sub>), 4 ml of Me<sub>2</sub>S, and 9.1 ml of Et<sub>2</sub>O,

was added, dropwise and with stirring, a solution of 99 mg (1.01 mmol) of the enone 4 in 4 ml of Et<sub>2</sub>O. The resulting solution, from which a red precipitate separated within 5 min, was stirred at -72° for 2 hr and then allowed to warm to 27° during 2 hr. After following the previously described isolation procedure, an aliquot of the crude product (164 mg of liquid) was mixed with a known weight of dicyclohexyl (an internal standard) for analysis [glpc, FFAP (Regis Chemical Co.) on Chromosorb P, apparatus calibrated with known mixtures]. The crude product contained the enone 4 (ret. time 3.2 min, 6% recovery), the ketone 29 (8.4 min, 1% yield), the alcohol 30 (15.1 min, 71% yield), and dicyclohexyl (25.5 min). A comparable reaction of 2.00 g (20.4 mmol) of the enone with a solution of (CH<sub>2</sub>=CHCH<sub>2</sub>)<sub>2</sub>CuLi [from 6.30 g (30.7 mmol) of Me<sub>2</sub>SCuBr and 61.3 mmol of CH<sub>2</sub>=CHCH<sub>2</sub>Li (from PhOCH<sub>2</sub>CH=CH<sub>2</sub>)] in 30 ml of Me<sub>2</sub>S and 40 ml of Et<sub>2</sub>O produced 3.27 g of crude liquid product containing (glpc) the alcohol 30 accompanied by minor amounts of the enone 4 and the ketone 29. A collected (glpc) sample of the ketone 29 was identified with an authentic sample by comparison of ir spectra and glpc retention times. Distillation of a 3.14-g aliquot of the crude product separated 1.96 g (72%) of the alcohol 30, bp 68-74° (10 mm),  $\underline{n}^{25}_{\underline{D}}$  1.4552 - 1.4585, that was identified with an authentic sample by comparison of ir and nmr spectra and glpc retention times.

Reaction of 2.76 g (28 mmol) of the enone 4 with 34 mmol of CH<sub>2</sub>=CHCH<sub>2</sub>MgBr in 48 ml of Et<sub>2</sub>O followed by the usual isolation procedure afforded 3.06 g (78%) of the alcohol 30 as a colorless liquid, bp 70-75° (10 mm),  $\underline{n}^{25}_{\underline{D}}$  1.4570 [lit.<sup>32</sup> bp 72° (18 mm),

$n_D^{20}$  1.4598]; ir ( $\text{CCl}_4$ ), 3600, 3570, 3460 (OH), 1666, 1639 (C=C), and  $922\text{ cm}^{-1}$  ( $\text{CH}=\text{CH}_2$ ); nmr ( $\text{CCl}_4$ ),  $\delta$  4.7 - 6.2 (4H, m, vinyl CH), 2.25 (2H, d,  $J = 7\text{ Hz}$ , allylic  $\text{CH}_2$ ), 1.83 (3H, d,  $J = 1\text{ Hz}$ , allylic  $\text{CH}_3$ ), 1.6 - 1.8 (1H, broad, OH), 1.66 (3H, d,  $J = 1\text{ Hz}$ , allylic  $\text{CH}_3$ ), and 1.25 (3H, s,  $\text{CH}_3$ ).

Anal. Calcd for  $\text{C}_9\text{H}_{16}\text{O}$ : C, 77.09; H, 11.50. Found: C, 76.96; H, 11.55.

Following a previously described<sup>15</sup> procedure, a solution of 1.00 g (8.8 mmol) of the silane 40 in 10 ml of  $\text{CH}_2\text{Cl}_2$  was added, dropwise and with stirring during 2 min, to a cold ( $-78^\circ$ ) mixture of 0.78 g (8.0 mmol) of the enone 4 and 1.52 g (8.0 mmol) of  $\text{TiCl}_4$  in 10 ml  $\text{CH}_2\text{Cl}_2$ . The resulting red-brown mixture was allowed to warm to  $25^\circ$  with stirring during 40 min and then partitioned between  $\text{H}_2\text{O}$  and  $\text{Et}_2\text{O}$ . The organic solution was dried and concentrated to leave 1.60 g of crude liquid product. After an aliquot of the crude product had been mixed with a known amount of 1,3,5-(i-Pr) $_3\text{C}_6\text{H}_3$  (an internal standard), analysis (glpc, Carbowax 20 M on Chromosorb P, apparatus calibrated with known mixtures) indicated the presence of the enone 4 (ret. time 12.8 min, 13% recovery), the ketone 29 (26.8 min, 85% yield), and 1,3,5-(i-Pr) $_3\text{C}_6\text{H}_3$  (108 min). Distillation of a 1.39-g aliquot of the crude product separated 641 mg (66%) of the ketone 29 as a colorless liquid, bp  $45-60^\circ$  (10 mm),  $n_D^{25}$  1.4330 [lit.<sup>33</sup> bp  $167-168^\circ$ ,  $n_D^{25}$  1.4335]; ir ( $\text{CCl}_4$ ), 1720 (C=O), 1639 (C=C), and  $922\text{ cm}^{-1}$  ( $\text{CH}=\text{CH}_2$ ); uv max (95% EtOH), 286 nm ( $\epsilon$  21); nmr ( $\text{CCl}_4$ ),  $\delta$  4.7 - 6.2 (3H, m, vinyl CH), 2.25 (2H, s,  $\text{CH}_2\text{CO}$ ), 1.9-2.2 (5H, m, allylic  $\text{CH}_2$  and  $\text{COCH}_3$ ), and 0.98 (6H, s,  $\text{CH}_3$ ); mass spectrum, m/e



(rel. intensity), 125 (7), 99 (46), 82 (75), 67 (33), 55 (28), 43 (100), 41 (36), and 39 (36).

C. With Enone 5. To a cold ( $-72^{\circ}$ ) suspension (the  $\text{Me}_2\text{SCuBr}$  was only partially dissolved at  $-72^{\circ}$ ) of 576 mg (2.80 mmol) of  $\text{Me}_2\text{SCuBr}$  in 6 ml of  $\text{Me}_2\text{S}$  and 6 ml of  $\text{Et}_2\text{O}$  was added, dropwise with stirring and cooling, a solution of 5.60 mmol of  $\text{CH}_2=\text{CHCH}_2\text{Li}$  [from  $(\text{CH}_2=\text{CHCH}_2)_4\text{Sn}$ ] in 5.2 ml of  $\text{Et}_2\text{O}$ . As the lithium reagent was added the white precipitate ( $\text{Me}_2\text{SCuBr}$ ) dissolved to give an orange-red solution and finally a pale yellow solution when all of the lithium reagent had been added. However, unlike the cuprate preparation using  $\text{CH}_2=\text{CHCH}_2\text{Li}$  from  $\text{PhOCH}_2\text{CH}=\text{CH}_2$ , no red precipitate was observed when equimolar amounts of  $\text{Me}_2\text{SCuBr}$  and  $\text{CH}_2=\text{CHCH}_2\text{Li}$  were present. To the cold ( $-72^{\circ}$ ) solution of the cuprate was added, dropwise and with stirring, a solution of 94.1 mg (1.12 mmol) of the enone 5 and 66.3 mg of  $n\text{-C}_{12}\text{H}_{26}$  (an internal standard) in 2 ml of  $\text{Et}_2\text{O}$ . During this addition the solution developed a red-orange color but no red precipitate was observed. The resulting solution was warmed to  $-50^{\circ}$ , stirred for 2 hr, warmed to  $-40^{\circ}$ , and siphoned into a cold ( $-40^{\circ}$ ), stirred solution of 3 ml of  $\text{HOAc}$  in 25 ml of  $\text{Et}_2\text{O}$ . (In other runs where the diallylcuprate reagent was allowed to warm to  $-30$  to  $-35^{\circ}$  before quenching, some thermal decomposition of the cuprate reagent was evident.) The resulting mixture was warmed to  $25^{\circ}$  and partitioned between  $\text{Et}_2\text{O}$  and aqueous  $\text{NaHCO}_3$ . After the ethereal layer had been washed successively with an aqueous solution (pH 8) of  $\text{NH}_3$  and  $\text{NH}_4\text{Cl}$  and with aqueous  $\text{NaCl}$ , it was dried and concentrated for glpc analysis (UCON 50HB 280X on

Chromosorb P, apparatus calibrated with known mixtures). The product contained the enone 5 (ret. time 3.4 min, 44% yield), the ketone 27 (7.6 min, 13% yield), the alcohol 28 (10.1 min, 16% yield), and  $n\text{-C}_{12}\text{H}_{26}$  (15.1 min). In a second comparable run where the reaction mixture was stirred at  $-55$  to  $-60^\circ$  for 45 min and then warmed to  $25^\circ$  before quenching, the yields were: 28% of enone 5, 18% of ketone 27, and 22% of alcohol 28. Collected (glpc) samples of ketones 5 and 27 and alcohol 28 were identified with authentic samples<sup>12</sup> by comparison of glpc retention times and ir spectra.

In an additional set of experiments  $\text{CH}_2=\text{CHCH}_2\text{Li}$ , prepared from  $\text{PhOCH}_2\text{CH}=\text{CH}_2$ , was used to prepare the diallylcuprate reagent. These preparations differed from the preparation described above in that a red precipitate separated when equimolar quantities of  $\text{Me}_2\text{SCuBr}$  and  $\text{CH}_2=\text{CHCH}_2\text{Li}$  were present and redissolved as the second equivalent of  $\text{CH}_2=\text{CHCH}_2\text{Li}$  was added to give a cold ( $-70$  to  $-72^\circ$ ) orange solution of the diallylcuprate reagent. From a series of reactions run for 2-3 hr within the temperature range  $-72$  to  $-30^\circ$  and then quenched in a  $\text{HOAc-Et}_2\text{O}$  mixture at  $-40$  to  $-30^\circ$ , the product yields were: 48-53% of enone 5, 10-16% of ketone 27, and 12-18% of alcohol 28.

A solution of 1.27 mmol of  $\text{CH}_2=\text{CHCH}_2\text{MgBr}$  in 1.73 ml of  $\text{Et}_2\text{O}$  was added, dropwise and with stirring, to a cold ( $-65^\circ$ ) suspension of 71.2 mg (0.35 mmol, 28 mmol %) of  $\text{Me}_2\text{SCuBr}$  in 3 ml of  $\text{Me}_2\text{S}$  and 3 ml of  $\text{Et}_2\text{O}$  and the resulting pale orange solution was stirred at  $-60$  to  $-65^\circ$  for 10 min. Then a solution 95.8 mg (1.14 mmol) of the enone 5 and 74.3 mg of  $n\text{-C}_{12}\text{H}_{26}$  (an internal standard) in 3 ml of

Et<sub>2</sub>O was added, dropwise and with stirring during 35 min while the temperature of the mixture was maintained at -48 to -52°. The resulting light orange suspension was stirred at -50° for 2 hr and then warmed to -40°, quenched in an HOAc-Et<sub>2</sub>O mixture at -40°, and subjected to the previously described isolation analysis procedures. The yields were 8% of enone 5, 20% of ketone 27, and 60% of alcohol 28. Collected (glpc) samples of the products were identified with authentic samples by comparison of ir and mass spectra and glpc retention times. In a similar reaction where an Et<sub>2</sub>O solution of CH<sub>2</sub>=CHCH<sub>2</sub>MgBr was added slowly to a cold (-72°) mixture of the enone 5 and 27 mol % of Me<sub>2</sub>SCuBr the yields were 4% of enone 5, 13% of ketone 27, and 53% of the alcohol 28.

### References and Notes

1. (a) For a recent review, see H. O. House, Accts. Chem. Res., 9, 59 (1976); (b) H. O. House, C. Y. Chu, J. M. Wilkins, and M. J. Umen, J. Org. Chem., 40, 1460 (1975); (c) H. O. House and C. Y. Chu, ibid., 41, 3083 (1976); (d) H. O. House and K. A. J. Snoble, ibid., 41, 3076 (1976); (e) H. O. House, A. V. Prabhu, J. M. Wilkins, and L. F. Lee, ibid., 41, 3067 (1976); (f) H. O. House, C. Y. Chu, W. V. Phillips, T. S. B. Sayer, and C. C. Yau, ibid., 42, 1709 (1977); (g) This thesis, Chapter II.
2. Although this reagent is now known to be dimeric ( $\text{Li}_2\text{Cu}_2\text{Me}_4$ ) in  $\text{Et}_2\text{O}$  solution, we will continue to represent this reagent as  $\text{LiCuMe}_2$  unless clarity of the discussion requires the dimeric formulation. Molecular weight studies of this reagent have been performed by (a) R. G. Pearson and C. D. Gregory [J. Am. Chem. Soc., 98, 4098 (1976)] and (b) E. C. Ashby and J. J. Watkins, ibid., 99, 5312 (1977).
3. H. O. House, L. E. Huber, and M. J. Umen, J. Am. Chem. Soc., 94, 8471 (1972).
4. H. O. House and J. M. Wilkins, J. Org. Chem., 41, 4031 (1976); This thesis, Chapter III-A.
5. G. H. Posner, C. E. Whitten, J. J. Sterling and D. J. Brunelle, Tetrahedron Lett., 2591 (1974).
6. W. H. Mandeville and G. M. Whitesides, J. Org. Chem., 39, 400 (1974). In similar competition reactions with the enone 4, the reactivity orders were  $n\text{-Bu} > \text{sec-Bu} > t\text{-Bu}$  with no adduct observed involving the addition of a  $t\text{-Bu}$  group.
7. K. Koosha, J. Berlan, M. L. Capmau, and W. Chodkiewicz, Bull. Soc. Chim. Fr., 1284 (1975).
8. For recent examples, see (a) H. O. House and J. C. DuBose, J. Org. Chem., 40, 788 (1975); (b) M. F. Semmelhack and R. D. Stauffer, ibid., 40, 3619 (1975); (c) T. Yoshida and E. Negishi, Chem. Commun., No. 18, 762 (1974); (d) E. C. Ashby and J. J. Lin, Tetrahedron Lett., No. 50, 4453 (1975); E. C. Ashby, J. J. Lin, and R. Kovar, J. Org. Chem., 41, 1939 (1976); (e) K. Wada, M. Tamura, and J. Kochi, J. Am. Chem. Soc., 92, 6656 (1970); (f) M. F. Semmelhack, R. D. Stauffer, and A. Yamashita, J. Org. Chem., 42, 3180 (1977).

9. (a) L. Mandell and J. M. Brodmann, J. Org. Chem., 31, 591 (1966); (b) H. O. House and W. F. Fischer, Jr., ibid., 34, 3615 (1969).
10. (a) E. S. Binkley and C. H. Heathcock, J. Org. Chem., 40, 2156 (1975); (b) A. E. Greene and P. Crabbé, Tetrahedron Lett., 4867 (1976).
11. (a) D. Seyferth and M. A. Weiner, Org. Syntheses, Coll. Vol. 5, 452 (1973); (b) J. J. Eisch and A. M. Jacobs, J. Org. Chem., 28, 2145 (1963).
12. H. O. House, C. Y. Chu, W. V. Phillips, T. S. B. Sayer, and C. C. Yau, J. Org. Chem., 42, 1709 (1977).
13. H. O. House, W. V. Phillips, T. S. B. Sayer, and C. C. Yau, J. Org. Chem., in press.
14. G. Daviaud and Ph. Miginiac, Tetrahedron Lett., 3345 (1973).
15. A. Hosomi and H. Sakurai, J. Am. Chem. Soc., 99, 1673 (1977).
16. All melting points are corrected and all boiling points are uncorrected. Unless otherwise stated  $\text{MgSO}_4$  was employed as a drying agent. The ir spectra were determined with a Perkin Elmer, Model 257, infrared recording spectrophotometer fitted with a grating. The uv spectra were determined with a Cary, Model 14, or a Perkin Elmer, Model 202, recording spectrophotometer. The proton nmr spectra were determined at 60 mHz with a Varian, Model A-60 or Model T-60-A, nmr spectrometer and the  $^{13}\text{C}$  nmr spectra were determined at 25 mHz with a JEOL Fourier transform spectrometer, Model PFT-100. The chemical shift values are expressed in  $\delta$  values (ppm) relative to a  $\text{Me}_4\text{Si}$  internal standard. The mass spectra were obtained with a Hitachi (Perkin Elmer), Model RMU-7, or a Varian, Model M-66, mass spectrometer. All reactions involving strong bases or reactive organometallic intermediates were performed under a nitrogen atmosphere.
17. H. C. Odom and A. R. Pinder, Org. Syntheses, 51, 115 (1971).
18. F. H. Stross, J. M. Monger, and H. de V. Finch, J. Amer. Chem. Soc., 69, 1627 (1947).
19. G. M. Whitesides, C. P. Casey, and J. K. Krieger, J. Amer. Chem. Soc., 93, 1379 (1971).
20. (a) O. Grummitt, E. P. Budewitz, and C. C. Chudd, Org. Syntheses, Coll. Vol. 4, 748 (1963); (b) J. C. H. Hwa, and H. Sims, ibid., Coll. Vol. 5, 608 (1973).

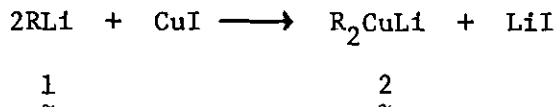
21. These measurements were performed in our laboratory by Mr. Ronald Sieloff.
22. (a) S. C. Watson and J. F. Eastham, J. Organometal. Chem., 9, 165 (1967); (b) M. Gall and H. O. House, Org. Syntheses, 52, 39 (1972).
23. (a) J. W. Wilt and A. Danielzadeh, J. Org. Chem., 23, 920 (1958); (b) A. Hoffman, J. Amer. Chem. Soc., 51, 2542 (1929).
24. (a) W. A. Mosher, P. W. Berger, A. P. Foldi, J. E. Gardner, T. J. Kelly, and C. Nebel, J. Chem. Soc., C, 121 (1969); (b) A. D. Grebenyuk and N. T. Zaitseva, Zh. Org. Khim., 4, 302 (1968); (c) J. Colonge and L. Pichat, Bull. Soc. Chim. Fr., 177 (1949).
25. I. N. Nazarov and Zh. A. Krasnaia, Izvest. Akad. Nauk S.S.S.R., Otdel. Khim. Nauk, 870 (1958); Chem. Abstr., 53, 1124e (1959).
26. F. C. Whitmore, D. P. J. Goldsmith, N. C. Cook, J. C. Yarze, and G. G. Ecke, J. Amer. Chem. Soc., 72, 53 (1950).
27. (a) A. D. Petrov, V. L. Sushchinsky, and L. D. Konovalchikov, Zhur. Obshchei Khim., 25, 1566 (1955); (b) H. Sliwa and P. Maitte, Bull. Soc. Chim. Fr., 369 (1962).
28. R. Ya. Levina, V. N. Kostin, P. A. Gembitskii, and E. G. Treshchova, J. Gen. Chem. USSR, 30, 883 (1960).
29. J. Royer and J. Dreux, Tetrahedron Lett., No. 53, 5589 (1968); Justus Liebigs Ann. Chem., 741, 109 (1970).
30. H. H. Stechl, Chem. Ber., 97, 2681 (1964).
31. (a) R. C. Huston and R. L. Guile, J. Am. Chem. Soc., 61, 69 (1939); (b) C. D. Nenitzescu and I. Chicos, Ber., 68, 1584 (1935); (c) L. E. Hightower, L. R. Glasgow, K. M. Stone, D. A. Albertson, and H. A. Smith, J. Org. Chem., 35, 1881 (1970).
32. H. R. Henze, B. B. Allen, and W. B. Leslie, J. Org. Chem., 7, 326 (1942).
33. A. Viola, E. J. Iorio, K. K. Chen, G. M. Glover, U. Nayak, and P. J. Kocienski, J. Am. Chem. Soc., 89, 3462 (1967).

## CHAPTER II

THE EFFECT OF SOLVENT ON THE  
 CONJUGATE ADDITION OF LITHIUM  
 DIORGANOCUPRATES TO ENONES

Introduction and Discussion

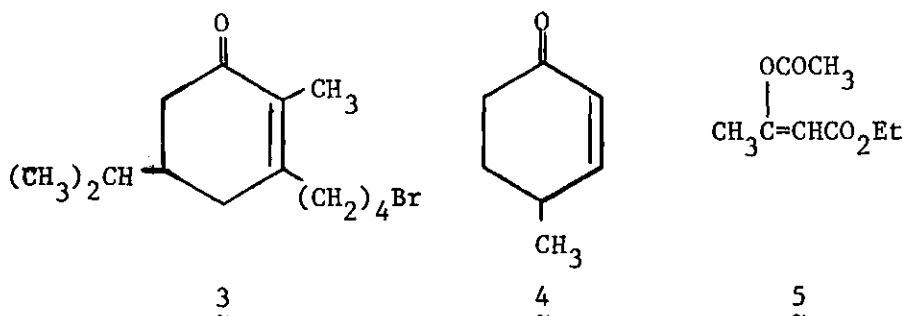
In selecting the reaction conditions to be used in a synthetic transformation involving a lithium diorganocuprate reagent  $\underline{2}$ ,<sup>1</sup> many chemists tend to select the reaction solvent either from consideration of the most convenient solvent for the organolithium reagent  $\underline{1}$  used to form the cuprate  $\underline{2}$  or in accord with the local custom in their laboratory. However, several studies<sup>1b,2</sup> have indicated a clear



increase in the rate of coupling reactions<sup>1b</sup> involving nucleophilic displacement at an alkyl halide by a cuprate cluster when a better donor solvent<sup>3</sup> (e.g. THF or an Et<sub>2</sub>O-HMP mixture) is used rather than either pure Et<sub>2</sub>O or an Et<sub>2</sub>O-hydrocarbon mixture. The analogous nucleophilic displacements by cuprates at alkyl tosylates<sup>2b</sup> and epoxides<sup>4</sup> exhibit the opposite solvent effect (faster in Et<sub>2</sub>O than in THF). This seemingly curious reversal is understandable if one considers that the departure of both of these oxygen-containing

leaving groups should be assisted by coordination with  $\text{Li}^+$  cation.<sup>4</sup> Although often disregarded, this  $\text{Li}^+$  cation is present as  $\text{LiI}$  (or  $\text{LiBr}$ ) in amounts comparable to the cuprate reagent 2 unless special steps are taken to remove it.<sup>2a,5</sup> Thus, if one considers that all cuprate nucleophilic displacements benefit by coordination of the cuprate cluster with a donor solvent but that this benefit is offset in displacements at epoxides and tosylates by coordination of  $\text{Li}^+$  cation with the donor solvent rather than the oxygen-containing leaving group, the above solvent effects are reasonable.<sup>4,6</sup> We now wish to call attention to the fact that a different and sometimes very important solvent effect is observed in the conjugate addition reactions of lithium diorganocuprate reagents 2 to enones.

As part of another study, Posner and co-workers reported<sup>7a</sup> that the addition of  $\text{Me}_2\text{CuLi}$  to the enone 3 (calcd.  $E_{\text{red}} -2.3\text{V}$ )<sup>8a</sup> became progressively slower (i.e. more starting material was recovered) as the solvent was changed from  $\text{PhH}$  to  $\text{Et}_2\text{O}$  to  $\text{THF}$ . More recently Ouannes and co-workers noted<sup>10</sup> that the conjugate additions



of  $\text{Me}_2\text{CuLi}$  to the enone 4 (calcd  $E_{\text{red}} -2.1\text{V}$ )<sup>8a</sup> and  $\text{Et}_2\text{CuLi}$  to the ester 5 (calcd  $E_{\text{red}} -2.3\text{V}$ )<sup>8</sup> were inhibited by the addition of 2-3 mol equiv of 12-crown-4 polyether and Ashby and co-workers noted<sup>11</sup> that

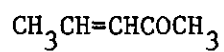
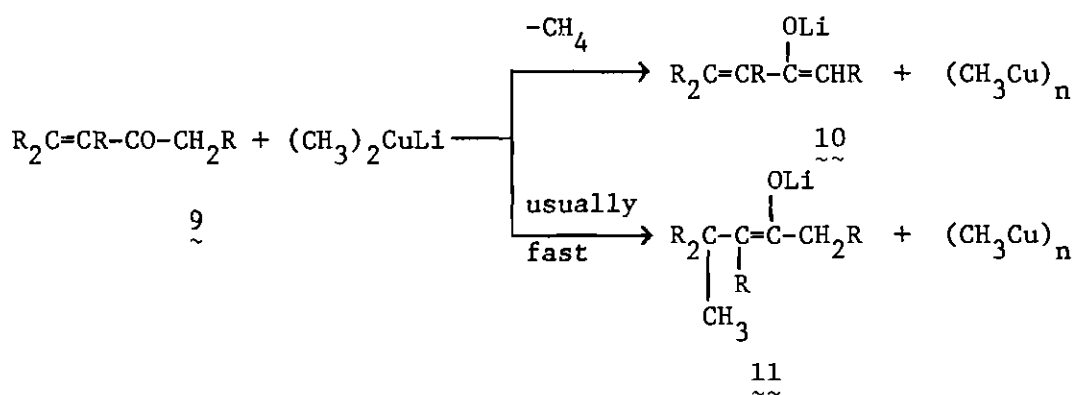
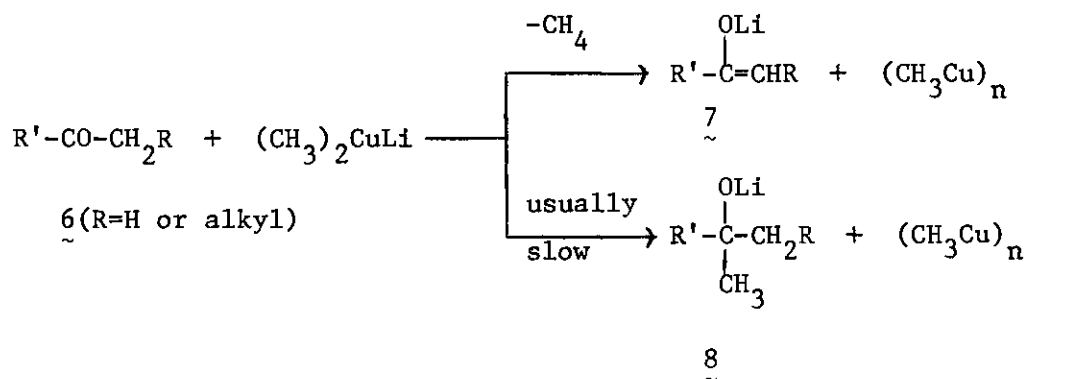


lower yields of conjugated addition products were obtained in THF than in Et<sub>2</sub>O when Me<sub>2</sub>CuLi was added to several different enones (calcd E<sub>red</sub> -2.1 to -2.2V).<sup>8a</sup>

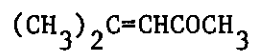
As we have noted elsewhere,<sup>9,12,13</sup> the rather common assumption that unchanged ketone recovered from a cuprate reaction represents lack of reaction is usually erroneous. Thus, non-conjugated ketones of the type 6 (Scheme I) react with Me<sub>2</sub>CuLi to form mainly the metal enolate 7 accompanied by a slow reaction to yield a 1,2-adduct 8. With ketones where formation of an enolate 7 is precluded the slow 1,2-addition becomes the major reaction.<sup>9,12</sup> A similar set of competing reactions occurs with conjugated enones of the type 9; the reaction differs only in the fact that rate of formation of the 1,4-adduct 11 is usually much more rapid than formation of the enolate 10. However, when the reduction potential of the enone 9 becomes sufficiently negative (typically more negative than -2.35V with Me<sub>2</sub>CuLi in Et<sub>2</sub>O solution), the rate of formation of the conjugate adduct 11 is markedly retarded and the competing formation of the metal enolate 10 becomes the dominant reaction.<sup>9</sup>

In view of these various observations, we were led to wonder whether a change to a better donor solvent was interfering with all conjugate addition reactions of cuprate reagents or only with those reactions in which the enone was relatively difficult to reduce (corresponding to a relatively negative reduction potential for the enones). To examine this question, each member of a series of enones 12-14 with increasingly negative reduction potentials was allowed to react with Me<sub>2</sub>CuLi in various reaction solvents. The

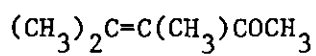
Scheme I



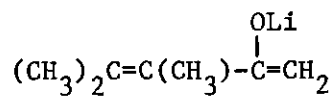
12 (E<sub>red</sub> -2.08V)



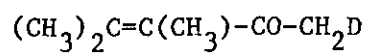
13 (E<sub>red</sub> -2.21V)



14 (E<sub>red</sub> -2.35V)



18



19

results, summarized in Table II-1, illustrate that for the most difficultly reduced enone 14, the yield of conjugate adduct 15 could be more than doubled by changing the solvent from pure Et<sub>2</sub>O to an Et<sub>2</sub>O-pentane mixture (1:5 v/v). Although the use of an even greater proportion of pentane might be expected to be beneficial, in practice we were unable to keep the cuprate reagent in solution when the proportion of pentane was increased beyond the 1:5 ratio indicated and, consequently, found no further improvement in yield. Diluting ethereal solutions of Me<sub>2</sub>CuLi with a better donor solvent, THF or DME, completely inhibited conjugate addition with the difficultly reduced enone 14. In these experiments a relatively slow reaction still occurred [precipitation of (CH<sub>3</sub>Cu)<sub>n</sub>] but the product was the enolate 18 that was reconverted to the starting ketone 14 by hydrolysis with H<sub>2</sub>O or to the monodeuterio ketone 19 by quenching in a D<sub>2</sub>O-DOAc mixture. The same enolate 18 was formed along with the enolate of the conjugate adduct 15 in our earlier study<sup>9</sup> of the reaction of the enone 14 with Me<sub>2</sub>CuLi in Et<sub>2</sub>O solution.

Although the enone 13 with an intermediate reduction potential was converted practically completely to the conjugate adduct 17 in Et<sub>2</sub>O solution, when mixtures of Et<sub>2</sub>O and a better donor solvent, THF or DME, were employed approximately equal amounts of conjugate addition and enolate formation were observed. Only with the most easily reduced enone 12 did we observe essentially complete formation of conjugate adduct 16 in both Et<sub>2</sub>O and in a better donor solvent containing mixture of Et<sub>2</sub>O and either THF or DME. Since it is possible to prepare stable solutions of Me<sub>2</sub>CuLi in a mixture of

Table II-1. Reaction of  $\text{Me}_2\text{CuLi}$  with the Enones 12-14 at 10-30° in Various Solvents

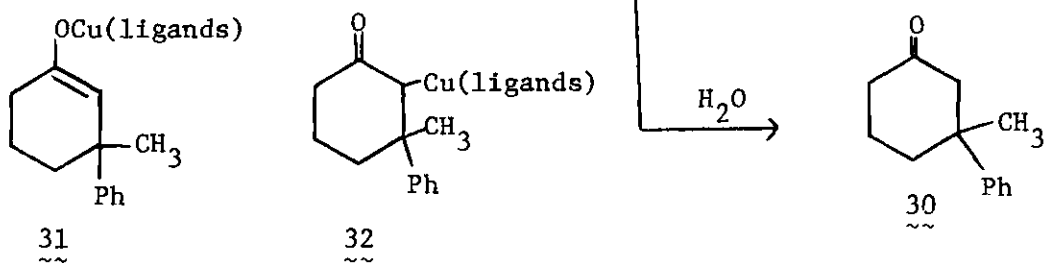
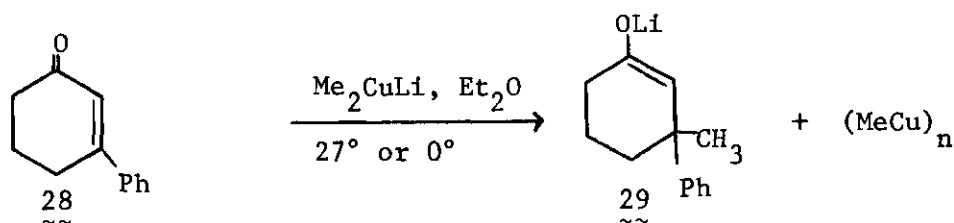
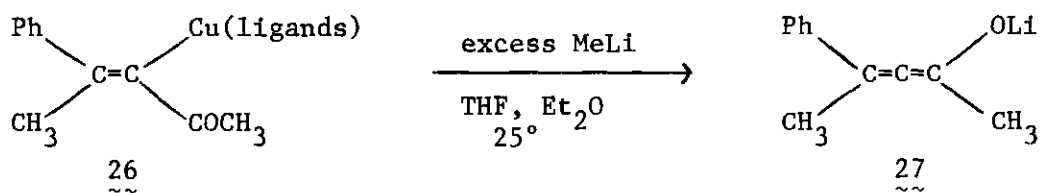
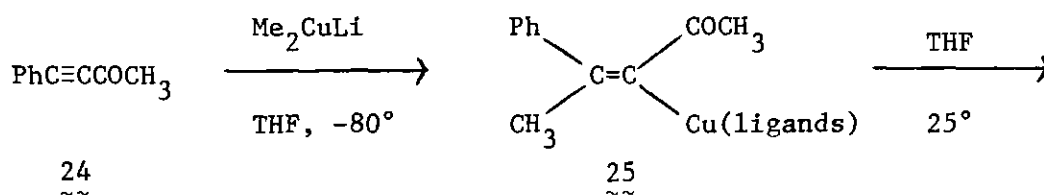
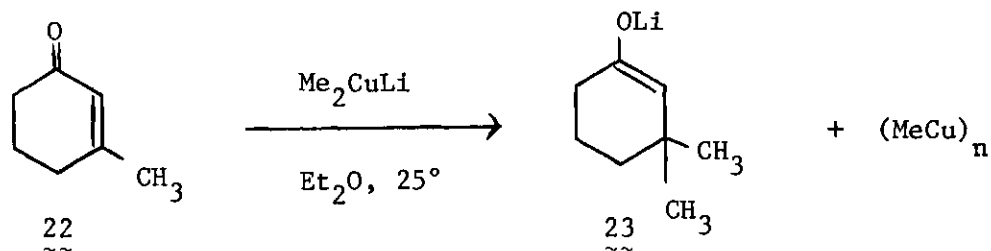
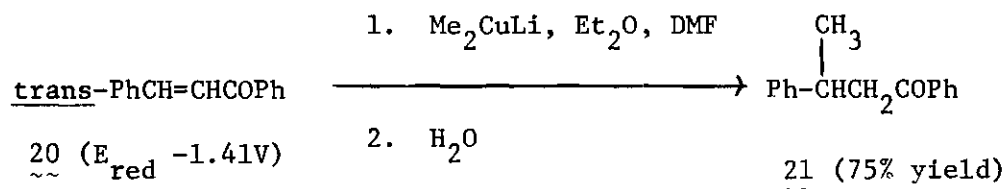
Solvent	Reaction product (% yield)		
	<u>trans</u> - $\text{CH}_3\text{CH}=\text{CHCOCH}_3$ <u>12</u> ( $E_{\text{red}} -2.08\text{V}$ )	$(\text{CH}_3)_2\text{C}=\text{CHCOCH}_3$ <u>13</u> ( $E_{\text{red}} -2.21\text{V}$ )	$(\text{CH}_3)_2\text{C}=\text{C}(\text{CH}_3)\text{COCH}_3$ <u>14</u> ( $E_{\text{red}} -2.35\text{V}$ )
$\text{Et}_2\text{O}$ -pentane (1:3.4 v/v)	--	$(\text{CH}_3)_3\text{CCH}_2\text{COCH}_3$ <u>17</u> (88%)	$(\text{CH}_3)_3\text{CCH}(\text{CH}_3)\text{COCH}_3$ + <u>14</u> (26%) <u>15</u> (59%)
$\text{Et}_2\text{O}$ -PhH (1:5 v/v)	--	--	<u>15</u> (37%) + <u>14</u> (62%)
$\text{Et}_2\text{O}$ - $\text{Me}_2\text{S}$ (1:5 v/v)	--	--	<u>15</u> (31%) + <u>14</u> (62%)
$\text{Et}_2\text{O}$ - $\text{CH}_2\text{Cl}_2$ (1:3.3 v/v)	--	--	<u>15</u> (25%) + <u>14</u> (63%)
$\text{Et}_2\text{O}$	$(\text{CH}_3)_2\text{CHCH}_2\text{COCH}_3$ <u>16</u> (94%) <sup>a</sup>	$(\text{CH}_3)_3\text{CCH}_2\text{COCH}_3$ <u>17</u> (93%)	<u>15</u> (21%) <sup>b</sup> + <u>14</u> (72%)
$\text{Et}_2\text{O}$ -THF (1:5 v/v)	<u>16</u> (98%)	<u>17</u> (51%) + <u>13</u> (39%)	<u>14</u> (96%)
$\text{Et}_2\text{O}$ -DME (1:5 v/v)	<u>16</u> (84%)	<u>17</u> (45%) + <u>13</u> (45%)	<u>14</u> (100%)

<sup>a</sup>This experiment was described by H. O. House, W. L. Respess, and G. M. Whitesides, *J. Org. Chem.*, **31**, 3128 (1966). <sup>b</sup>This experiment was originally reported in Ref. 9; the range of product compositions was 15-30% of 15 and 70-85% of 14.

Et<sub>2</sub>O and DMF,<sup>13</sup> it was also of interest to examine the behavior of enones with Me<sub>2</sub>CuLi in the presence of the very effective donor solvent, DMF.<sup>3</sup> We did not detect any conjugate adduct 16 or 17 from reaction of Me<sub>2</sub>CuLi with either of the enones 12 or 13 in an Et<sub>2</sub>O-DMF solution. However, by employing the much more easily reduced (and difficultly enolizable<sup>14a</sup>) enone 20 (Scheme II), the conjugate adduct 21 was formed even in Et<sub>2</sub>O-DMF solution (1:3 v/v). It is clear, therefore, that in the competitive reactions of an enone 9 with a cuprate to form either an enolate 10 or a conjugate adduct 11, the conjugate addition is disfavored by the presence of good donor solvents.

In the previous discussion, the initial 1,4-addition products (e.g. 11) have been formulated as lithium enolates based on the observation<sup>14b</sup> that the enone 22 (Scheme II) reacts at 25° with an Et<sub>2</sub>O solution containing one mol-equiv of Me<sub>2</sub>CuLi to form a mixture of a yellow precipitate of (MeCu)<sub>n</sub> that contains practically all of the copper and an Et<sub>2</sub>O solution of the enolate 23 that contains essentially none of the copper. Several studies<sup>14c</sup> of acetylenic ketones, esters, and acids have demonstrated somewhat different behavior when these acetylenic derivatives react with cuprate reagents. For example, the ketone 24 reacted with Me<sub>2</sub>CuLi in THF at -80° to form a vinylcopper derivative 25 that underwent stereochemical isomerization to a solution of the more stable vinylcopper derivative 26 at 25°. Treatment with excess MeLi at 25° converted the vinylcopper derivative 26 to the lithium enolate 27. To explore the possibility that even olefinic ketones might initially

## Scheme II



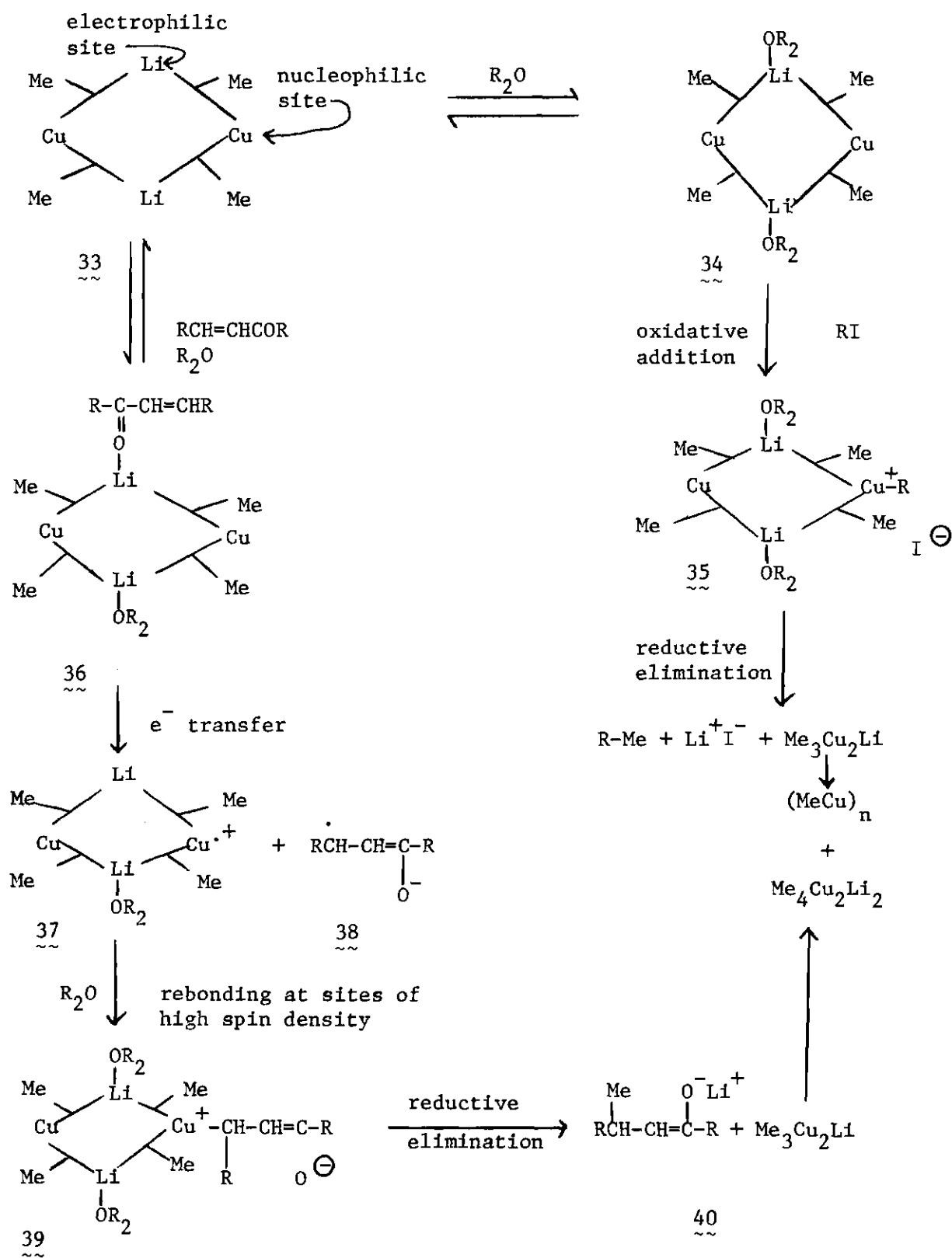
form covalent copper(I) derivatives that are subsequently converted to lithium enolates such as 23, we examined the reaction of a rather reactive enone 28 (calcd  $E_{\text{red}}$  -1.7V)<sup>8a</sup> with ethereal  $\text{Me}_2\text{CuLi}$  at several temperatures. At both 27° and 0°, the results paralleled the earlier study<sup>14b</sup> with enone 22 in that essentially all of the copper and none of the enolate 29 were present in the  $(\text{MeCu})_n$  precipitate. At lower temperatures (-44° and -72°) the study was complicated by a combination of the reaction being incomplete and partial crystallization of the starting enone 28 from the reaction solution. However, in all cases the bulk of the copper (94% or more) was in the precipitate and only at -72° was the bulk of the enolate in the precipitate. We did observe that reaction of the enone 28 with  $\text{Me}_2\text{CuLi}$  at -72° produced an initial orange-colored precipitate that changed to the yellow-colored precipitate characteristic of  $(\text{MeCu})_n$  as the mixture was warmed to 0°. Thus, it is possible that at low reaction temperatures an insoluble covalent copper species such as 31 or 32 may be formed. However our evidence argues against the presence of stable, soluble species of these types unlike the situation with the vinylcopper derivatives (e.g. 26) formed from acetylenic compounds.

The foregoing data indicate that reactions of lithium diorganocuprates involving nucleophilic displacement at alkyl halides are favored by the presence of donor solvents while conjugate addition reactions of cuprates to enones are disfavored by such solvents even though the presence of  $\text{Li}^+$  cation (from  $\text{LiI}$  or  $\text{LiBr}$ ) is not required for successful cuprate-enone reactions.<sup>5</sup> For

example, comparable amounts of 1,4-adduct 15 were formed from reaction of the enone 14 in Et<sub>2</sub>O solution with either the usual Me<sub>2</sub>CuLi reagent (containing a full mol-equivalent of dissolved LiBr) or with a solution Me<sub>2</sub>CuLi reagent that had been prepared by a procedure<sup>2a,5</sup> that removed 95% of the dissolved lithium halide. We suggest the following working hypothesis to account for the differing solvent effects in these two cuprate reactions. With the dimeric<sup>15</sup> cuprate cluster 33 (Scheme III) it is probable that the Li atoms serve as relatively hard electrophilic sites for coordination with relatively hard nucleophiles (e.g. Et<sub>2</sub>O or other hard donor ligands) while the Cu atoms serve as relatively soft nucleophilic sites for bonding with relatively soft electrophiles (e.g. alkyl halides).<sup>2a,b,15a,16</sup> Since the oxidative addition of the alkyl halide to the metal cluster 34 → 35 (or nucleophilic displacement at the alkyl halide by the metal cluster) should be facilitated by prior coordination with donor ligands 33 → 34 to increase the electron density in the metal cluster, the increased rate of this nucleophilic displacement in the presence of good donor solvents (e.g. THF, HMP) is reasonable. A variety of evidence has been accumulated<sup>12,13,17,18</sup> to support the idea that a pair of ion radical intermediates 37 and 38 are formed prior to bonding of the enone to the metal cluster to form an intermediate 39 leading to the conjugate adduct 40. Certain of these studies<sup>13</sup> provided clear evidence for the reversible formation of a coordination complex (such as structure 36) between the ketone and the cuprate cluster prior to electron transfer and suggested the need to form this



Scheme III



complex  $\sim\sim$  36 in order for a subsequent inner-sphere electron transfer to occur producing ion radicals  $\sim\sim$  37 and  $\sim\sim$  38. The presence of a good donor solvent,  $R_2O$ , in the reaction mixture would favor the conversion of the cuprate cluster  $\sim\sim$  33 to its solvate  $\sim\sim$  34 and would, consequently, tend to diminish the concentration of the enone-cuprate complex  $\sim\sim$  36 needed for electron transfer and subsequent conjugate addition  $\sim\sim$  39  $\rightarrow$   $\sim\sim$  40. With difficultly reduced enones where the electron transfer step  $\sim\sim$  36  $\rightarrow$   $\sim\sim$  38 is not especially favorable, the result of diminishing the concentration of complex  $\sim\sim$  36 would be to decrease the rate of conjugate additions allowing the usually slower competing enolate formation to become the dominant reaction. Although it is not presently clear what cuprate species is primarily responsible for the conversion of ketones to their metal enolates, it is apparent that this competing reaction is not inhibited by the presence of good donor solvents.

Irrespective of the validity of the above hypothesis, there are several practical consequences of these solvent effects that can be of considerable importance in the use of lithium diorganocuprates as synthetic intermediates. In any reaction where the reduction potential of the enone is sufficiently negative that conjugate addition of a cuprate is likely to be difficult ( $-2.3V$  for  $Me_2CuLi$  and  $-2.1$  to  $-2.4V$  for other lithium diorganocuprates<sup>19</sup>), the presence of a good donor solvent (e.g. THF or DME) is clearly undesirable. In such cases the best yields of conjugate adduct are likely to be obtained by employing an  $Et_2O$ -pentane (or hexane) mixture as the reaction solvent. Since a change in solvents can modify the reactivity

of the cuprate reagent toward conjugate addition, it should be possible with a substrate containing both an easily reduced enone and a difficultly reduced enone system to choose a reaction solvent that will allow selective conjugate addition to only the more easily reduced enone. Of perhaps more value is the possibility that a substrate containing both a displaceable C-halogen grouping and an enone system would undergo a selective nucleophilic displacement by a cuprate reagent at the C-halogen bond (normally a slow reaction) by selecting a solvent that would inhibit the normally rapid conjugate addition to the enone system.

### Experimental Section<sup>20</sup>

#### Preparation of Reagents

All solvents were purified by distillation from  $\text{LiAlH}_4$  immediately before use. Recrystallized samples of  $\text{Me}_2\text{SCuBr}$ <sup>9</sup> were used to prepare all organocopper(I) derivatives. The  $\text{Me}_2\text{S}$  was purified by distillation from  $\text{LiAlH}_4$ , b.p. 36-38°. Pure samples of enones 12<sup>21</sup> and 14<sup>9</sup> were obtained as previously described and a pure sample of enone 13 was obtained by fractional distillation<sup>22</sup> of commercial mesityl oxide, b.p. 127-128°,  $n_{\text{D}}^{25}$  1.4430 (lit.<sup>22</sup> b.p. 129.8°,  $n_{\text{D}}^{20}$  1.44575). Solutions of halide-free  $\text{MeLi}$ , obtained by reaction of  $\text{MeCl}$  with  $\text{Li}$  dispersion in  $\text{Et}_2\text{O}$ , were standardized by a double titration procedure<sup>23</sup> in which aliquots of the reagent, both before and after reaction with  $\text{BrCH}_2\text{CH}_2\text{Br}$ , were titrated with standard aqueous acid. Alternatively, the  $\text{MeLi}$  solutions were standardized by titration with sec-BuOH employing 2,2'-bipyridyl

as the indicator.<sup>24</sup>

Titration for halide ion by the Volhard procedure indicated that the LiCl content of the halide-free MeLi was 5-6 mol %.

#### Preparation of the Enone 28

Following a previously described procedure,<sup>25</sup> a solution of 15.0 g (110 mmol) of the 3-ethoxy-2-cyclohexenone in 80 ml of Et<sub>2</sub>O was added during 2 hr to 100 ml of an Et<sub>2</sub>O solution containing the PhMgBr from 29.9 g (191 mmol) of PhBr and 4.80 g (198 mg-atom) of Mg. After the reaction mixture had been hydrolyzed with dilute aqueous H<sub>2</sub>SO<sub>4</sub> and steam distilled to remove Ph-Ph and unchanged PhBr, it was extracted with Et<sub>2</sub>O and the ethereal extract was washed successively with aqueous NaHCO<sub>3</sub> and with H<sub>2</sub>O, decolorized with charcoal, dried, and concentrated. The residual yellow solid was recrystallized from petroleum ether (b.p. 30-60°) to separate 14.8 g (78%) of the enone 28 as pale yellow plates, mp 61-62° (lit. mp 61-61.5°, <sup>26</sup> 64.5-66°<sup>25</sup>); ir (CCl<sub>4</sub>), 1670 cm<sup>-1</sup> (C=O); nmr (CCl<sub>4</sub>), δ 7.1-7.7 (5H, m, aryl CH), 6.26 (1H, partially resolved multiplet, vinyl CH), and 1.9-2.9 (6H, m, aliphatic CH); uv max (95% EtOH), 217.5 nm (ε 9180) and 283.5 nm (ε 17,000); mass spectrum, m/e (rel. intensity), 172 (M<sup>+</sup>, 99), 145 (25), 144 (100), 128 (20), 116 (70), 115 (72), and 102 (21).

#### Reaction of Me<sub>2</sub>CuLi with the Enone 28

To a cold (0°) solution of Me<sub>2</sub>CuLi, from 358 mg (1.74 mmol) of Me<sub>2</sub>SCuBr, 3.48 mmol of halide-free MeLi, and 12 ml of Et<sub>2</sub>O was added, dropwise and with stirring, a solution of 198 mg (1.15 mmol) of the enone 28 in 4 ml of Et<sub>2</sub>O. After the resulting red-orange

solution, from which a yellow precipitate separated rapidly, had been stirred at 0° for 1 hr, it was siphoned into a vigorously stirred aqueous solution (pH 8) of  $\text{NH}_4\text{Cl}$  and  $\text{NH}_3$ . The resulting solution was extracted with  $\text{Et}_2\text{O}$  and the ethereal extract was dried, concentrated, and mixed with a known weight of *o*-terphenyl (an internal standard) for glpc analysis (silicone SE-52 on Chromosorb P, apparatus calibrated with known mixtures). The crude product contained the ketone 30 (ret. time 12.8 min, 96% yield) and *o*-terphenyl (37.0 min) but none of the starting enone 28 (17.7 min) was detected. A collected (glpc) sample of the ketone 30 was obtained as a colorless liquid,  $n_D^{25}$  1.5397 [lit.<sup>27</sup> bp 80-100° (0.1 mm)]; ir ( $\text{CCl}_4$ ), 1719  $\text{cm}^{-1}$  (C=O); nmr ( $\text{CCl}_4$ ),  $\delta$  7.0-7.4 (5H, m, aryl CH), 1.4-3.0 (8H, m,  $\text{CH}_2$ ), and 1.26 (3H, s,  $\text{CH}_3$ , lit.<sup>31</sup> 1.28); uv (95% EtOH), series of weak maxima ( $\epsilon$  283 or less) in region 247-268 nm with a maximum at 282 nm ( $\epsilon$  87); mass spectrum, m/e (rel. intensity), 188 ( $\text{M}^+$ , 65), 173 (30), 145 (30), 131 (100), 118 (50), 117 (33), 91 (51), 55 (68), and 42 (43).

In a series of similar experiments, solutions of 1.16-1.18 mmol of the enone 28 in 5 ml of  $\text{Et}_2\text{O}$  were added, dropwise and with stirring during a period of 40-45 min, to centrifuge tubes containing 1.22-1.28 mmol of  $\text{Me}_2\text{CuLi}$  in 6.5 ml of  $\text{Et}_2\text{O}$  that were continuously cooled in baths at the temperatures indicated in Table II-2. In each case a yellow (27°, 0°, -44°) to orange (-72°) precipitate separated during the addition of the enone 28. The resulting mixtures were stirred for 40 min at the bath temperatures indicated in Table II-2, centrifuged for 1-2 min, and again stored in the cooling baths while

the supernatant liquid was separated from each tube with a cannula. In the experiments performed at 27° and at 0°, the precipitates were washed with two 10-ml portions of Et<sub>2</sub>O (at 0° or 27°) and these washings were combined with the appropriate supernatant solutions. The separate supernatant solutions and precipitates were each hydrolyzed with water and extracted with Et<sub>2</sub>O. Each of the Et<sub>2</sub>O extracts was dried, concentrated, mixed with a known weight of o-terphenyl, and subjected to the previously described glpc analysis. Each aqueous phase was acidified with aqueous H<sub>2</sub>SO<sub>4</sub> and HNO<sub>3</sub>, boiled to complete the oxidation of all Cu salts to Cu(II) salts and to expel oxides of nitrogen, and then analyzed for copper by electro-deposition. The yields of Cu, the recovered enone 28, and the ketone 30, found in the precipitates and the supernatant solutions are presented in Table II-2. It will be noted that throughout the

Table II-2. Reaction of Enone 28 With Me<sub>2</sub>CuLi in Et<sub>2</sub>O Solution

Bath Temperature, °C	Product Yields, %					
	Supernatant Solution			Precipitate		
	Cu	Enone <u>28</u>	Ketone <u>30</u>	Cu	Enone <u>28</u>	Ketone <u>30</u>
27°	0.5	15	72	99	—	—
0°	1.5	17	68	98	—	—
-44°	1.2	4	67	98	3	17
-72°	5.3	9	0.5	94	59	32

temperature range examined ( $-72^{\circ}$  to  $27^{\circ}$ ) practically all of the Cu containing materials were in the precipitate. The bulk of the metal enolate of ketone 30 (along with a substantial amount of unchanged enone 28) was found in the precipitate only at the lowest temperature ( $-72^{\circ}$ ) examined.

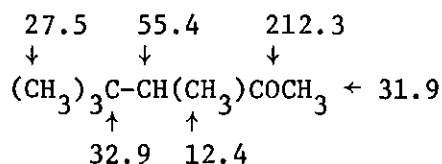
To explore the solubility of the Li enolate 29 at low temperature, the above reaction of  $\text{Me}_2\text{CuLi}$  with the enone 28 was repeated at  $27^{\circ}$  and the supernatant solution was separated from the  $(\text{MeCu})_n$  precipitate by centrifugation. When this supernatant solution was cooled to  $0^{\circ}$ , a small amount of grey-white solid precipitated. This precipitate was separated by centrifugation, hydrolyzed, and subjected to the previously described glpc analysis. The organic material obtained from this precipitate contained the enone 28 (0.4% recovery) and the ketone 30 (0.4% yield). The remaining solution was cooled to  $-72^{\circ}$  and centrifuged to separate a white crystalline precipitate (mainly LiBr) from a pale yellow supernatant solution. The organic material obtained from this precipitate contained the enone 28 (1.1% recovery) and the ketone 30 (0.7% yield). The supernatant solution was hydrolyzed to give the enone 28 (22% recovery) and the ketone 30 (55% yield). Thus, we conclude that the Li enolate 29 is relatively soluble in  $\text{Et}_2\text{O}$  at  $-72^{\circ}$  in the concentration range where these experiments were performed.

#### Reactions of $\text{Me}_2\text{CuLi}$ With the Enone 14 in Various Solvents

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Solutions of  $\text{Me}_2\text{CuLi}$  prepared from 411 mg (2.0 mmol) of  $\text{Me}_2\text{S-CuBr}$  and 2.4 ml of  $\text{Et}_2\text{O}$  containing 4.0 mmol of halide-free

MeLi, were stirred at 10-25° for 5 min and then diluted either with 12 ml of Et<sub>2</sub>O or with the appropriate volume (see Table II-1) of one of the purified co-solvents, pentane, PhH, Me<sub>2</sub>S, CH<sub>2</sub>Cl<sub>2</sub>, THF, or DME. Then weighed samples of the enone 14 (ca. 112 mg or 1 mmol) and n-C<sub>12</sub>H<sub>26</sub> (ca. 100 mg, internal standard) in 2.0 ml of the co-solvent were added and the reaction mixtures were stirred for 12 hr at 25-30°. After the mixtures had been treated with a limited amount of H<sub>2</sub>O (ca. 0.3 ml) and then filtered, the resulting organic solutions were analyzed by glpc [FFAP (Regis Chemical Co.) on Chromosorb P, apparatus calibrated with known mixtures]; the retention times were: ketone 15, 8.7 min; enone 14, 18.6 min; n-C<sub>12</sub>H<sub>26</sub>, 36.8 min. Collected (glpc) samples of the ketones 14 and 15 (n<sup>25</sup>D 1.4152, lit. n<sup>25</sup>D 1.4161,<sup>28</sup> 1.4162<sup>9</sup>) were identified with authentic samples<sup>9</sup> by comparison of ir, nmr, and mass spectra and glpc retention times. The <sup>13</sup>C nmr spectrum of the ketone 15 (CDCl<sub>3</sub> solution) is summarized in the following structure; the indicated assignments are consistent with off-resonance decoupling measurements. The yields of ketone 15 and recovered enone 14 from the various reactions are summarized in Table II-1.



A cold (15°) solution of Me<sub>2</sub>CuLi, from 3.717 g (18.1 mmol) of Me<sub>2</sub>SCuBr, 36.2 mmol of MeLi (halide-free) in 25 ml of Et<sub>2</sub>O,



and 125 ml of THF, was treated with a solution of 1.021 g (9.12 mmol) of the enone 14 in 10 ml of THF. The originally colorless solution progressively turned yellow, pink, and then violet and yellow (MeCu)<sub>n</sub> began to precipitate after 10 min. After the reaction mixture had been stirred at 15-20° for 1 hr, it was added, slowly with stirring, to a solution of DOAc and D<sub>2</sub>O prepared by refluxing a mixture of 7.91 g (77.6 mmol) of freshly distilled Ac<sub>2</sub>O and 10 ml of D<sub>2</sub>O. The resulting mixture was filtered and extracted with three 25-ml portions of Et<sub>2</sub>O. After the combined ethereal extracts had been washed with aqueous NaHCO<sub>3</sub>, dried, and concentrated, an aliquot of the crude liquid product (1.92 g) was mixed with a known weight of n-C<sub>12</sub>H<sub>26</sub> for glpc analysis. The calculated recovery of the enone 19 (or 14) was 85% and none of the conjugate adduct 15 was detected. Short-path distillation of the remaining crude product separated 686 mg of the enone 19 containing (mass spectral analysis) 15% d<sub>0</sub> species, 78% d<sub>1</sub> species, and 7% d<sub>2</sub> species. The nmr spectrum (CCl<sub>4</sub>) of this product corresponded to the nmr spectrum of the enone 14 except that the CH<sub>3</sub>CO singlet at δ 2.10 was largely replaced by a three-line pattern (J<sub>HD</sub> = 2.2 Hz) at slightly higher field (δ 2.08)<sup>29</sup> corresponding to the COCH<sub>2</sub>D grouping. In a second comparable experiment, the recovered enone 19 (86% yield) contained (mass spectral analysis) 22% d<sub>0</sub> species and 78% d<sub>1</sub> species and exhibited nmr absorption comparable to that described above. As a control experiment, 755 mg (6.74 mmol) of the enone 14 in 5 ml of THF was added to a solution prepared from 10.1 mmol of Me<sub>2</sub>CuLi, 78 ml of THF, 43 mmol of CH<sub>3</sub>CO<sub>2</sub>D, and 10 ml of D<sub>2</sub>O. After

the resulting mixture had been stirred at 27° for 2 hr, the previously described isolation procedure was used to separate 491 mg of the enone 14, bp 49-50° (12 mm), that contained (mass spectral analysis) 99% d<sub>0</sub> species and 1% d<sub>1</sub> species.

The following experiments were performed to compare the reaction of enone 14 with ethereal Me<sub>2</sub>CuLi in the presence and absence of dissolved Li<sup>+</sup> salts. A solution of 84 mg (0.75 mmol) of the enone 14 and 60 mg of n-C<sub>12</sub>H<sub>26</sub> in 4 ml of Et<sub>2</sub>O was added to a cold (6°) solution of 1.69 mmol of Me<sub>2</sub>CuLi and 1.69 mmol of LiBr [from 348 mg (1.69 mmol) of Me<sub>2</sub>SCuBr and 3.38 mmol of halide-free MeLi in 8.2 ml of Et<sub>2</sub>O]. The resulting mixture was allowed to warm from 6° to 22° with stirring during 20 min and quenched with H<sub>2</sub>O and analyzed (glpc, UCON 50HB 280X on Chromosorb P, apparatus calibrated with known mixtures). The crude product contained ketone 15 (ret. time 7.1 min, 19% yield), enone 14 (12.1 min, 80% yield) and n-C<sub>12</sub>H<sub>26</sub> (28.5 min). In a second comparable reaction the yields were 22% of ketone 15 and 69% of enone 14.

Reaction of 1.03 g (5.00 mmol) of Me<sub>2</sub>SCuBr with 4.96 mmol of halide-free MeLi in 9.2 ml of Et<sub>2</sub>O yielded a slurry of yellow (MeCu)<sub>n</sub> that was centrifuged. After the supernatant liquid had been separated, the (MeCu)<sub>n</sub> precipitate was washed with one 6-ml portion of Et<sub>2</sub>O and then treated with 4.65 mmol of halide-free MeLi in 9 ml of Et<sub>2</sub>O. Aliquots of the resulting Me<sub>2</sub>CuLi solution (0.53 M) were quenched in aqueous H<sub>2</sub>SO<sub>4</sub>, filtered, and titrated for halide content by the Volhard procedure; in a series of cuprate preparations, the halide concentration (mainly LiCl) was 0.023-

0.030 M (4-6 mol %). After a solution of 2.65 mmol of this halide-free  $\text{Me}_2\text{CuLi}$  in 9 ml of  $\text{Et}_2\text{O}$  had been allowed to react with 84 mg (0.75 mmol) of the enone 14 as previously described, the product yields (glpc analysis) were 17% of ketone 15 and 81% enone 14. From a second comparable run, the yields were 17% of ketone 15 and 77% of enone 14. Thus, in all of the reactions of enone 14 with  $\text{Me}_2\text{CuLi}$  in  $\text{Et}_2\text{O}$  solution the product was composed of 18-24% of the conjugate adduct 15 and 76-82% of the enone 14 (from enolate formation) irrespective of whether the solution contained a molar equivalent of LiBr.

#### Reaction of $\text{Me}_2\text{CuLi}$ With Enones 12 and 13

Solutions of  $\text{Me}_2\text{CuLi}$ , from 411 mg (2.0 mmol) of  $\text{Me}_2\text{S-CuBr}$  and 2.4 ml of an  $\text{Et}_2\text{O}$  solution containing 4.0 mmol of MeLi, were diluted with 11 ml of either THF or DME and then treated with 2.0 ml of the same co-solvent containing weighed amounts of  $n\text{-C}_{12}\text{H}_{26}$  (ca. 80-90 mg, internal standard) and either enone 13 (ca. 98 mg, 1.0 mmol) or 12 (ca. 84 mg, 1.0 mmol). The resulting mixtures were stirred at 25-30° for 12 hr and then subjected to the previously described isolation and analytical procedures. The glpc retention times (Carbowax 20M on Chromosorb P) for reactions with the enone 13 were: ketone 17, 16.1 min; enone 13, 29.9 min;  $n\text{-C}_{12}\text{H}_{26}$ , 58.9 min. The corresponding values for reactions with the enone 12 were: ketone 16, 13.9 min;  $n\text{-C}_{12}\text{H}_{26}$ , 55.8 min. Collected (glpc) samples of the ketones 13, 16, and 17 were identified with authentic samples<sup>31</sup> by comparison of glpc retention times and ir and either nmr or mass spectra. Comparable reaction and analysis procedures

were used for the reaction of 1.024 mmol of the enone 13 with 2.05 mmol of  $\text{Me}_2\text{CuLi}$  in 8.7 ml of  $\text{Et}_2\text{O}$  and for the reaction of 0.997 mmol of the enone 13 with 2.76 mmol of  $\text{Me}_2\text{CuLi}$  in a mixture of 3.6 ml of  $\text{Et}_2\text{O}$  and 14 ml of pentane. The yields of the ketones 16 and 17 and the recovered enone 13 are summarized in Table II-1.

#### Reaction of $\text{Me}_2\text{CuLi}$ With the Enone 20 in $\text{Et}_2\text{O}$ - DMF Solution

A solution of  $\text{Me}_2\text{CuLi}$ , prepared from 520 mg (2.53 mmol) of  $\text{Me}_2\text{SCuBr}$  and 4.95 mmol of  $\text{MeLi}$  (halide-free) in 3 ml of  $\text{Et}_2\text{O}$ , was diluted with 15 ml of anhydrous DMF and then a solution of 256 mg (1.23 mmol) of the enone 20 in 2 ml of  $\text{Et}_2\text{O}$  was added dropwise with stirring. The resulting solution, which turned red immediately upon addition of the enone, was stirred at  $25^\circ$  for 5 hr; during this period the initial red solution turned green within ca. 10 min but no further change and no precipitation of  $(\text{MeCu})_n$  was evident. The resulting mixture was partitioned between pentane and an aqueous solution of  $\text{NH}_4\text{Cl}$  and  $\text{NH}_3$ . The organic layer was washed with aqueous  $\text{NaCl}$ , dried, and concentrated to leave 345 mg of crude solid product containing (tlc, silica gel coating with an  $\text{Et}_2\text{O}$ -hexane eluent, 1:4 v/v) the adduct 21 ( $R_f$  0.43) and two minor unidentified impurities ( $R_f$  0.10 and 0.26). A 183.8-mg aliquot of the crude product was subjected to preparative tlc to separate 104.1 mg (75% yield) of the adduct 21 as colorless plates, mp  $70\text{--}72^\circ$  [lit.<sup>31</sup> mp  $70.5\text{--}71^\circ$ ]; the product was identified with an authentic sample by comparison of ir, nmr, and mass spectra.

### References and Notes

1. (a) G. H. Posner, Org. Reactions, 19, 1 (1972); (b) G. H. Posner, ibid., 22, 253 (1975).
2. (a) G. M. Whitesides, W. F. Fischer, Jr., J. San Filippo, Jr., R. W. Bashe, and H. O. House, J. Am. Chem. Soc., 91, 4871 (1969); (b) C. R. Johnson and G. A. Dutra, ibid., 95, 7777, 7783 (1973); (c) G. Linstrumelle, J. K. Krieger, and G. M. Whitesides, Org. Syntheses, 55, 103 (1976).
3. M. Szwarc in "Ions and Ion Pairs in Organic Reactions," Vol. 1, M. Szwarc, Ed., Wiley-Interscience, New York, N.Y., 1972, pp 1-6.
4. C. R. Johnson, R. W. Herr, and D. M. Wieland, J. Org. Chem., 38, 4263 (1973).
5. H. O. House and W. F. Fischer, Jr., J. Org. Chem., 33, 949 (1968).
6. The same consideration could be used to explain the rate retardation observed (Ref. 2b) in the reaction of  $\text{Me}_2\text{CuLi}$  with  $n\text{-C}_8\text{H}_{17}\text{OTs}$  when excess alkyl tosylate was present.
7. (a) G. H. Posner, J. J. Sterling, C. E. Whitten, C. M. Lentz, and D. J. Brunelle, J. Am. Chem. Soc., 97, 107 (1975); (b) G. H. Posner, C. E. Whitten, and J. J. Sterling, ibid., 95, 7788 (1973).
8. (a) The reduction potentials vs SCE in an aprotic solvent for the various carbonyl compounds were estimated as previously described; H. O. House, L. E. Huber, and M. J. Umen, J. Am. Chem. Soc., 94, 8471 (1972); (b) Comparison of the reduction potentials for  $\text{CH}_3\text{CH}=\text{CHCOCH}_3$  (-2.08V) and  $\text{CH}_3\text{C(OCOCH}_3)=\text{CHCOCH}_3$  (-2.14V, Ref. 9) suggests that a  $\beta\text{-OCOCH}_3$  substituent has about the same effect on the reduction potential as a  $\beta\text{-H}$  substituent. The reduction potential of the unsaturated ester 5 was estimated on this basis.
9. H. O. House, C. Y. Chu, J. M. Wilkins, and M. J. Umen, J. Org. Chem., 40, 1460 (1975).
10. C. Ouannes, G. Dressaire, and Y. Langlois, Tetrahedron Lett., 815 (1977).
11. E. C. Ashby, J. J. Lin, and J. J. Watkins, J. Org. Chem., 42, 1099 (1977).

12. H. O. House, A. V. Prabhu, J. M. Wilkins, and L. F. Lee, J. Org. Chem., 41, 3067 (1976).
13. H. O. House and C. Y. Chu, J. Org. Chem., 41, 3083 (1976).
14. (a) H. O. House and P. D. Weeks, J. Am. Chem. Soc., 97, 2785 (1975); (b) H. O. House and J. M. Wilkins, J. Org. Chem., 41, 4031 (1976); This thesis, Chapter III-A; (c) J. Klein and R. Levene, J. Chem. Soc., Perkin II, 1971 (1973) and references cited therein.
15. (a) R. G. Pearson and C. D. Gregory, J. Am. Chem. Soc., 98, 4098 (1976); (b) E. C. Ashby and J. J. Watkins, ibid., 99, 5312 (1977).
16. (a) The gold atom is the nucleophilic site in the reaction of the lithium dimethylaurate complex  $\text{Me}_2\text{Au}(\text{PPh}_3)\text{Li}$  with  $\text{MeI}$ ; A. Tamaki and J. Kochi, J. Chem. Soc., Dalton, 2620 (1973); (b) For a recent review of organogold compounds, see H. Schmidbaur, Angew Chem., Int. Ed. Engl., 15, 728 (1976).
17. For a recent review, see H. O. House, Accts. Chem. Res., 9, 59 (1976).
18. H. O. House and K. J. Snoble, J. Org. Chem., 41, 3076 (1976).
19. This thesis, Chapter I.
20. All melting points are corrected and all boiling points are uncorrected. Unless otherwise stated  $\text{MgSO}_4$  was employed as a drying agent. The ir spectra were determined with a Perkin Elmer, Model 257, infrared recording spectrophotometer fitted with a grating. The uv spectra were determined with a Cary, Model 14, or a Perkin Elmer, Model 202, recording spectrophotometer. The proton nmr spectra were determined at 60 MHz with a Varian, Model A-60 or Model T-60-A, nmr spectrometer and the  $^{13}\text{C}$  nmr spectra were determined at 25 MHz with a JEOL Fourier transform spectrometer, Model PFT-100. The chemical shift values are expressed in  $\delta$  values (ppm) relative to a  $\text{Me}_4\text{Si}$  internal standard. The mass spectra were obtained with a Hitachi (Perkin Elmer), Model RMU-7, or a Varian, Model M-66, mass spectrometer. All reactions involving strong bases or reactive organometallic intermediates were performed under a nitrogen atmosphere.
21. H. C. Odom and A. R. Pinder, Org. Syntheses, 51, 115 (1971).
22. F. H. Stross, J. M. Monger, and H. de V. Finch, J. Am. Chem. Soc., 69, 1627 (1947).

23. G. M. Whitesides, C. P. Casey, and J. K. Krieger, J. Am. Chem. Soc., 93, 1379 (1971).
24. (a) S. C. Watson and J. F. Eastham, J. Organometal. Chem., 9, 165 (1967); (b) M. Gall and H. O. House, Org. Syntheses, 52, 39 (1972).
25. G. F. Woods and I. W. Tucker, J. Am. Chem. Soc., 70, 2174 (1948).
26. H. O. House and R. L. Wasson, J. Am. Chem. Soc., 79, 1488 (1957).
27. J. R. Bantick and E. Rothstein, J. Chem. Soc., (C), 2512 (1971).
28. W. H. Saunders, Jr., and G. L. Carges, J. Am. Chem. Soc., 82, 3582 (1960).
29. This deuterium isotope effect on the position of an  $^1\text{H}$  nmr signal has been noted previously; G. Van Dyke Tiers, J. Chem. Phys., 963 (1958).
30. H. O. House, A. V. Prabhu, J. M. Wilkins, and L. F. Lee, J. Org. Chem., 41, 3067 (1976).
31. H. O. House and M. J. Umen, J. Org. Chem., 38, 3893 (1973).

## CHAPTER III

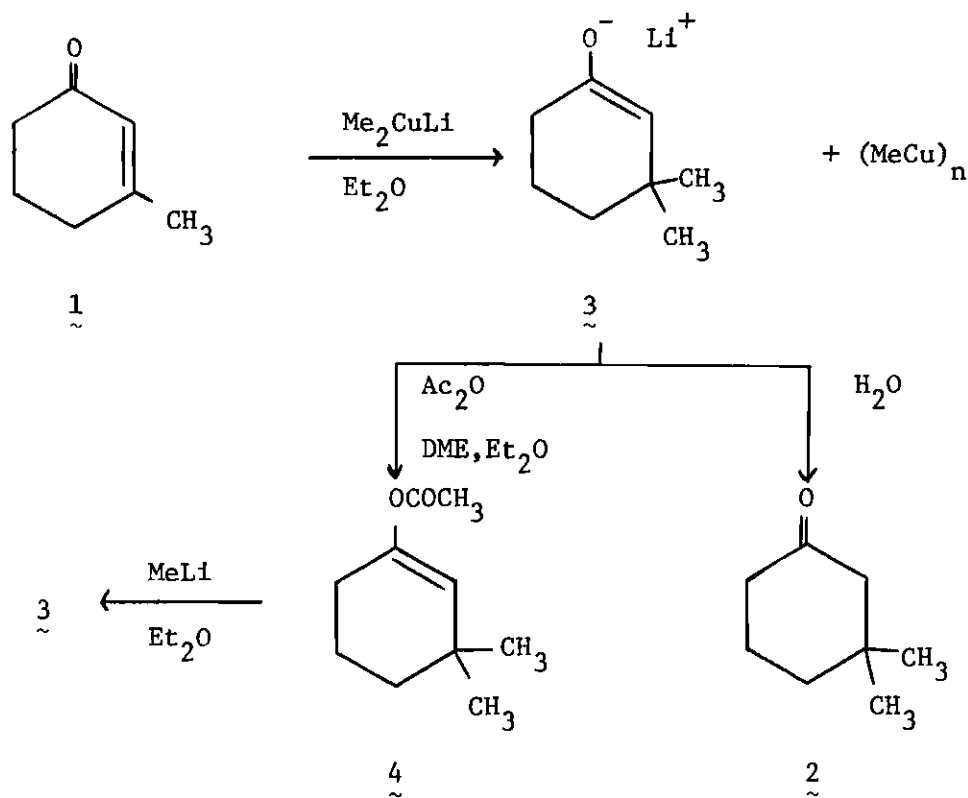
PART A. THE NATURE OF THE ENOLATE FORMED BY ADDITION  
OF LITHIUM DIMETHYLCUPRATE TO ENONESIntroduction and Discussion

The conjugate addition of lithium diorganocuprates to  $\alpha,\beta$ -unsaturated carbonyl compounds<sup>1</sup> produces, prior to hydrolysis, an intermediate with the properties of a metal enolate. Thus, reaction of this intermediate with  $\text{Ac}_2\text{O}$  yields an enol acetate,<sup>2</sup> reaction with  $\text{Me}_3\text{SiCl}$  yields a trimethylsilyl enol ether,<sup>3</sup> and reaction with a  $\text{ClPO}(\text{OEt})_2$  yields an enol phosphate.<sup>4</sup> Furthermore, this reaction intermediate reacts with carbonyl compounds to give aldol products,<sup>5</sup> with Michael acceptors to form Michael adducts,<sup>6</sup> and with reactive alkyl halides to form alkylated ketones.<sup>3b,7</sup> This reaction intermediate has been variously formulated as a lithium enolate,<sup>1b</sup> a copper(I) enolate,<sup>6,7a,b</sup> or as a species with the copper bound either to the  $\alpha$ -carbon atom or to both the oxygen atom and the  $\text{C}=\text{C}$  of the enolate.<sup>2b</sup>

Several observations led us to believe that these reaction intermediates were best formulated as lithium enolates rather than copper derivatives. The addition of 1 equiv of the soluble copper(I) derivative  $(\text{n-Bu}_2\text{S})_2\text{CuI}$  to a solution of the enolate  $\text{PhC}(\text{OLi})=\text{CH}_2$  did not alter the reactivity of this enolate in a Michael reaction.<sup>8</sup> Also, the addition of 1 equiv of the same soluble copper(I) derivative



did not alter the  $^1\text{H}$  nmr spectrum of the lithium enolate  $\text{PhC(OLi)=CHCl}$ .<sup>9</sup> Furthermore, in typical reactions of lithium dialkylcuprates (e.g.  $\text{Me}_2\text{CuLi}$ ) with enones, the reaction is accompanied by precipitation of the insoluble alkylcopper(I) derivative [e.g.  $(\text{MeCu})_n$ ] suggesting that the copper does not remain in solution with the intermediate enolate. However, all of the above observations leave some ambiguity about the nature of the reaction intermediate and yet this reaction intermediate is attaining increasing importance as a synthetic intermediate.<sup>2-7</sup> Consequently, it was clearly desirable to provide unambiguous information concerning this intermediate.



To provide this information in a typical reaction, the enone 1 was added to an  $\text{Et}_2\text{O}$  solution containing 1 equiv of  $\text{Me}_2\text{CuLi}$ . The resulting slurry was centrifuged to separate about 75% of the reaction mixture, a colorless supernatant liquid, from the lower portion of the reaction mixture which contained all the yellow  $(\text{MeCu})_n$  precipitate. Analysis of aliquots of each portion of the reaction mixture indicated that more than 99% of all the copper employed in the reaction was in the lower portion containing the  $(\text{MeCu})_n$  precipitate. A second aliquot of the supernatant solution exhibited  $^{13}\text{C}$  nmr absorption corresponding to an  $\text{Et}_2\text{O}$  solution of a lithium enolate.<sup>10</sup> After the remaining supernatant solution had been hydrolyzed, the amount of ketone 2 isolated corresponded to a 66% yield of this product from the supernatant solution.

In another experiment, the total reaction mixture from the enone 1 and  $\text{Me}_2\text{CuLi}$  was added to excess  $\text{Ac}_2\text{O}$  to form the expected<sup>2</sup> enol acetate 4 in 76% yield. Reaction of this enol acetate 4 with an ethereal solution containing 2 equiv of  $\text{MeLi}$  afforded an  $\text{Et}_2\text{O}$  solution of the lithium enolate 3 whose  $^{13}\text{C}$  nmr spectrum corresponded to the spectrum of the solution obtained from the cuprate reaction. Therefore, it is clear that conjugate addition of ethereal  $\text{Me}_2\text{CuLi}$  to the enone 1 forms the lithium enolate 3 and not some other intermediate in which the enolate is associated with a copper(I) species. It is very probable that the same conclusion applies to any conjugate addition of a cuprate reagent  $\text{R}_2\text{CuLi}$  that yields a soluble metal enolate along with an insoluble  $\text{RCu}$  product. Even in cases where the organocopper product  $\text{RCu}$  remains in the reaction

solution, our earlier nmr and reactivity studies<sup>8,9</sup> offer no evidence to support the view that lithium enolates interact with soluble copper(I) species to form copper(I) enolates.

### Experimental Section<sup>11</sup>

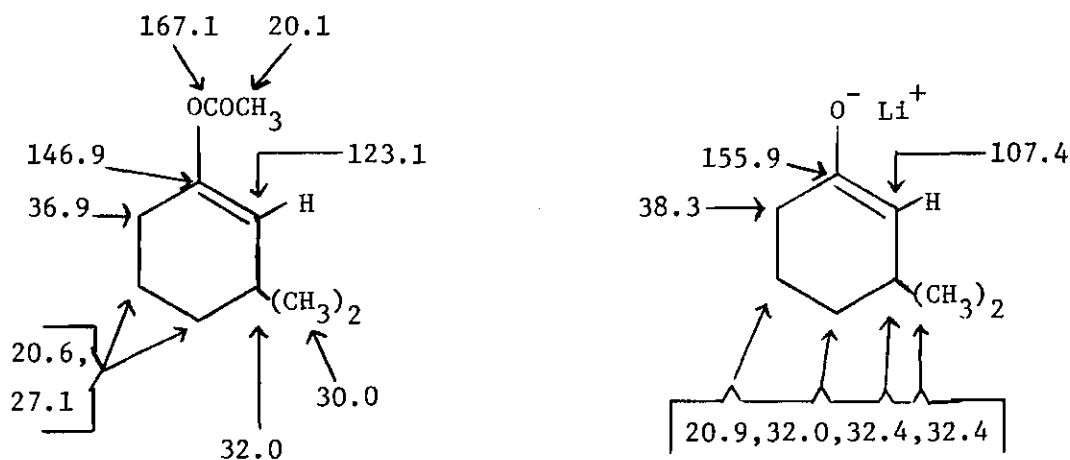
#### Preparation of the Enol Acetate 4 and the Lithium Enolate 3

After a solution of  $\text{Me}_2\text{CuLi}$ , prepared from 9.64 g (46.9 mmol) of  $\text{Me}_2\text{SCuBr}$  in 25 ml of  $\text{Me}_2\text{S}$  and 53 ml of an  $\text{Et}_2\text{O}$  solution containing 93.8 mmol of halide-free  $\text{MeLi}$ , had been stirred at  $27^\circ$  for 5 min, a solution of 3.93 g (35.8 mmol) of the enone 1 in 12 ml of  $\text{Et}_2\text{O}$  was added dropwise and with stirring during 10 min. The resulting mixture [containing solid  $(\text{MeCu})_n$ ] was stirred for 20 min and then added with stirring to a solution of 18.3 g (179 mmol) of freshly distilled  $\text{Ac}_2\text{O}$  in 35 ml of DME. After the resulting slurry had been stirred at  $27^\circ$  for 30 min, it was partitioned between pentane and saturated aqueous  $\text{NaHCO}_3$  and the organic phase was separated, dried, and concentrated. After an aliquot of the crude product had been mixed with a known weight of t-BuPh, analysis (glpc, Carbowax 20M on Chromosorb P) indicated the presence of t-BuPh (ret. time 3.8 min) and the enol acetate 4 (8.8 min, calculated yield 96%); neither the enone 1 (16.5 min) nor the ketone 2 (6.5 min) was detected in the glpc analysis. Distillation of the crude product separated 4.54 g (75.5%) of the enol acetate 4 as a colorless liquid, bp  $35\text{--}37^\circ$  (0.4 mm),  $n_D^{25}$  1.4500; ir ( $\text{CCl}_4$ ) 1754 (ester C=O) and  $1689\text{ cm}^{-1}$  (C=C); uv (95% EtOH), end absorption with  $\epsilon$  1580 at  $210\text{ m}\mu$ ; nmr ( $\text{CCl}_4$ ),  $\delta$  5.05 (1H, broad, vinyl CH), 1.2–2.3 (9H, m, aliphatic CH including a  $\text{CH}_3\text{CO}$  singlet at 1.99), and 1.02 (6H, s,  $\text{CH}_3$ ); mass

spectrum, m/e (re. intensity), 168 ( $M^+$ , 5), 126 (12), 111 (100), 55 (13), 43 (30), and 41 (11).

Anal. Calcd for  $C_{10}H_{16}O_2$ : C, 71.39; H, 9.59. Found: C, 71.38; H, 9.58.

To obtain an authentic sample of the enolate 3, 678 mg (4.04 mmol) of the enol acetate 4 was added, dropwise and with stirring, to 5.02 ml of a cold (10°)  $Et_2O$  solution containing 8.88 mmol of halide-free MeLi. After the resulting pale yellow solution had been stirred at 20° for 5 min, a 2.3-ml aliquot was mixed with 0.2 ml of  $Me_4Si$  and 0.2 ml of  $C_6D_6$  (to provide a "lock" signal) and the natural abundance  $^{13}C$  nmr signal was determined. For comparison the natural abundance  $^{13}C$  nmr spectrum of the enol acetate 4 was also determined in  $Et_2O$  containing  $Me_4Si$  and  $C_6D_6$ . These  $^{13}C$  nmr spectra (assignments consistent with off-resonance decoupling measurements and previous<sup>10</sup> analogous measurements) are summarized in the following structures. The  $^{13}C$  nmr spectrum of the enolate 3 also exhibited a peak at 35.0 ppm attributable<sup>10</sup> to the Me groups of  $t-BuOLi$ ; the second  $^{13}C$  nmr signal for this material was not resolved from the  $Et_2O$  peak at 65.8 ppm. It will be noted that the chemical shift difference ( $\Delta \delta$ ) between the  $\alpha$ -carbon atoms of the enol acetate 4 and the lithium enolate 3 in an  $Et_2O$  solution is 15.7 ppm, a value considerably smaller than the  $\Delta \delta$  values (21.5 to 22.5 ppm) observed for similar lithium enolates in DME or THF solution.<sup>10</sup>



#### Reaction of the Enone 1 with Me<sub>2</sub>CuLi

To 5.00 g (24.3 mmol) of Me<sub>2</sub>SCuBr was added, dropwise with stirring and cooling to 18–20°, 27.5 ml of an Et<sub>2</sub>O solution containing 48.7 mmol of halide-free MeLi. The enone 1 (2.55 g or 23.2 mmol) was added to this solution of Me<sub>2</sub>CuLi dropwise and with stirring during 15 min. The reaction mixture, from which yellow (MeCu)<sub>n</sub> began to precipitate within a few seconds after addition of the enone began, was stirred at 20–25° for 20 min and then centrifuged. The colorless supernatant solution (23.2 ml) was separated and the

residue [a mixture of solid  $(\text{MeCu})_n$  and the remaining reaction solution] was quenched in dilute aqueous  $\text{HNO}_3$ . Analysis of an aliquot of this aqueous solution by electrodeposition indicated the total copper content of the residue to be 24.3 mg-atom. Three 1.00-ml aliquots of the supernatant solution were each quenched in dilute aqueous  $\text{HNO}_3$  and then analyzed by electrodeposition; from these analyses, the copper content of the total supernatant solution was found to be 0.047 mg-atom. A 2.00-ml aliquot of the supernatant solution was mixed with 0.2 ml of  $\text{C}_6\text{D}_6$  and 0.2 ml of  $\text{Me}_4\text{Si}$  in order to determine the  $^{13}\text{C}$  nmr spectrum. This spectrum exhibited peaks corresponding to  $\text{Et}_2\text{O}$  (15.4 and 65.8 ppm),  $\text{Me}_2\text{S}$  (17.9 ppm), and to the previously described enolate 3. The positions of the "carbonyl" carbon and  $\alpha$ -carbon  $^{13}\text{C}$  signals of this enolate (156.2 and 105.4 ppm) differed slightly from the spectrum of the enolate 3 described above reflecting the facts that the concentrations of the two solutions were different and that one solution contained an equimolar amount of  $t\text{-BuOLi}$  while the other solution contained equimolar amounts of  $\text{LiBr}$  and  $\text{Me}_2\text{S}$ . However, in all other respects, the two enolate  $^{13}\text{C}$  nmr spectra were the same.

The remaining 18.2-ml aliquot of the supernatant liquid was partitioned between aqueous  $\text{NaHCO}_3$  and pentane. After the organic layer had been dried and concentrated, distillation of the residual liquid separated 1.51 g (corresponding to a 66% yield of ketone 2 in the supernatant solution) of the pure (glpc) ketone 2 as a colorless liquid, bp  $47\text{--}49^\circ$  (5 mm),  $n_{\text{D}}^{25}$  1.4454

[lit.<sup>12</sup> bp 74-74.5° (16 mm),  $\underline{n}^{25}_D$  1.4458], that was identified with an authentic sample<sup>12</sup> by comparison of ir and nmr spectra.

### References and Notes

1. (a) G. H. Posner, Org. Reactions, 19, 1 (1972); (b) H. O. House, Accts. Chem. Res., 9, 59 (1976).
2. (a) H. O. House, W. L. Respass, and G. M. Whitesides, J. Org. Chem., 31, 3128 (1966); (b) H. Riviere and P. W. Tang, Bull. Soc. Chim. Fr., 2455 (1973); (c) D. J. Goldsmith and I. Sakano, Tetrahedron Lett., No. 33, 2857 (1974).
3. (a) E. S. Binkley and C. H. Heathcock, J. Org. Chem., 40, 2156 (1975); (b) G. H. Posner, J. J. Sterling, C. E. Whitten, C. M. Lentz, and D. J. Brunelle, J. Am. Chem. Soc., 97, 107 (1975).
4. (a) R. E. Ireland and G. Pfister, Tetrahedron Lett., No. 26, 2145 (1969); (b) D. C. Muchmore, Org. Syntheses, 52, 109 (1972).
5. (a) G. Stork and M. Isobe, J. Am. Chem. Soc., 97, 6260 (1975); (b) F. Näf, R. Decorzant, and W. Thommen, Helv. Chim. Acta, 58, 1808 (1975); (c) K. K. Heng and R. A. J. Smith, Tetrahedron Lett., No. 8, 589 (1975).
6. R. K. Boeckman, Jr., J. Am. Chem. Soc., 95, 6867 (1973); ibid., 96, 6179 (1974).
7. (a) R. K. Boeckman, Jr., J. Org. Chem., 38, 4450 (1973); (b) R. M. Coates, and L. O. Sandefur, ibid., 39, 275 (1974); (c) J. W. Patterson, Jr., and J. H. Fried, ibid., 39, 2506 (1974).
8. H. O. House and W. F. Fischer, Jr., J. Org. Chem., 34, 3615 (1969).
9. H. O. House, W. F. Fischer, Jr., M. Gall, T. E. McLaughlin, and N. P. Peet, J. Org. Chem., 36, 3429 (1971).
10. H. O. House, A. V. Prabhu, and W. V. Phillips, J. Org. Chem., 41, 1209 (1976).
11. All boiling points are uncorrected. Unless otherwise stated MgSO<sub>4</sub> was employed as a drying agent. The ir spectra were determined with a Perkin Elmer, Model 257, infrared recording spectrophotometer fitted with a grating. The uv spectra were determined with a Perkin Elmer, Model 202, recording spectrophotometer. The proton nmr spectra were determined at 60 mHz with a Varian, Model A-60 or Model T-60-A, nmr



spectrometer and the  $^{13}\text{C}$  nmr spectra were determined at 100 MHz with a JEOL Fourier transform spectrometer, Model PFT-100. The chemical shift values are expressed in  $\delta$  values (ppm) relative to a  $\text{Me}_4\text{Si}$  internal standard. The mass spectra were obtained with an Hitachi (Perkin Elmer), Model RMU-7, or a Varian, Model M-66, mass spectrometer. All reactions involving strong bases or reactive organometallic intermediates were performed under a nitrogen atmosphere.

12. H. O. House and E. F. Kinloch, J. Org. Chem., 39, 1173 (1974).

PART B. THE REACTION OF LITHIUM DIMETHYLCUPRATE  
WITH ALKYL ARYL KETONES

Introduction and Discussion

Previous study<sup>1</sup> of the reaction of  $\text{Me}_2\text{CuLi}$  with carbonyl compounds revealed that  $\alpha,\beta$ -unsaturated carbonyl compounds having reduction potentials within the range  $-1.4$  to  $-2.35\text{V}$  (vs sce in an aprotic solvent) could be expected to react by way of an initial electron-transfer step to form products derived from the net conjugate addition of a methyl anion to the unsaturated carbonyl compound. Substrates with less negative reduction potentials (more easily reduced) yielded reduction rather than addition products while substrates with more negative reduction potentials (more difficultly reduced) either failed to react with  $\text{Me}_2\text{CuLi}$  or reacted, with liberation of  $\text{CH}_4$ , to form the metal enolate of the starting unsaturated ketone. Saturated ketones (which have reduction potentials more negative than  $-2.9\text{V}$ ) reacted with  $\text{Me}_2\text{CuLi}$  either with evolution of  $\text{CH}_4$  to form the metal enolates of the ketones or by a very slow process leading to 1,2-addition.<sup>1c</sup>

Since aryl alkyl ketones typically have reduction potentials in the range  $-1.8$  to  $-2.2\text{V}$  (vs sce in an aprotic solvent),<sup>2</sup> these compounds appeared to be substrates that might react with  $\text{Me}_2\text{CuLi}$  by a process that involved an initial electron transfer step. To learn what types of products might result, we have studied the reaction of  $\text{Me}_2\text{CuLi}$  with three types of aryl alkyl ketone systems 1-3

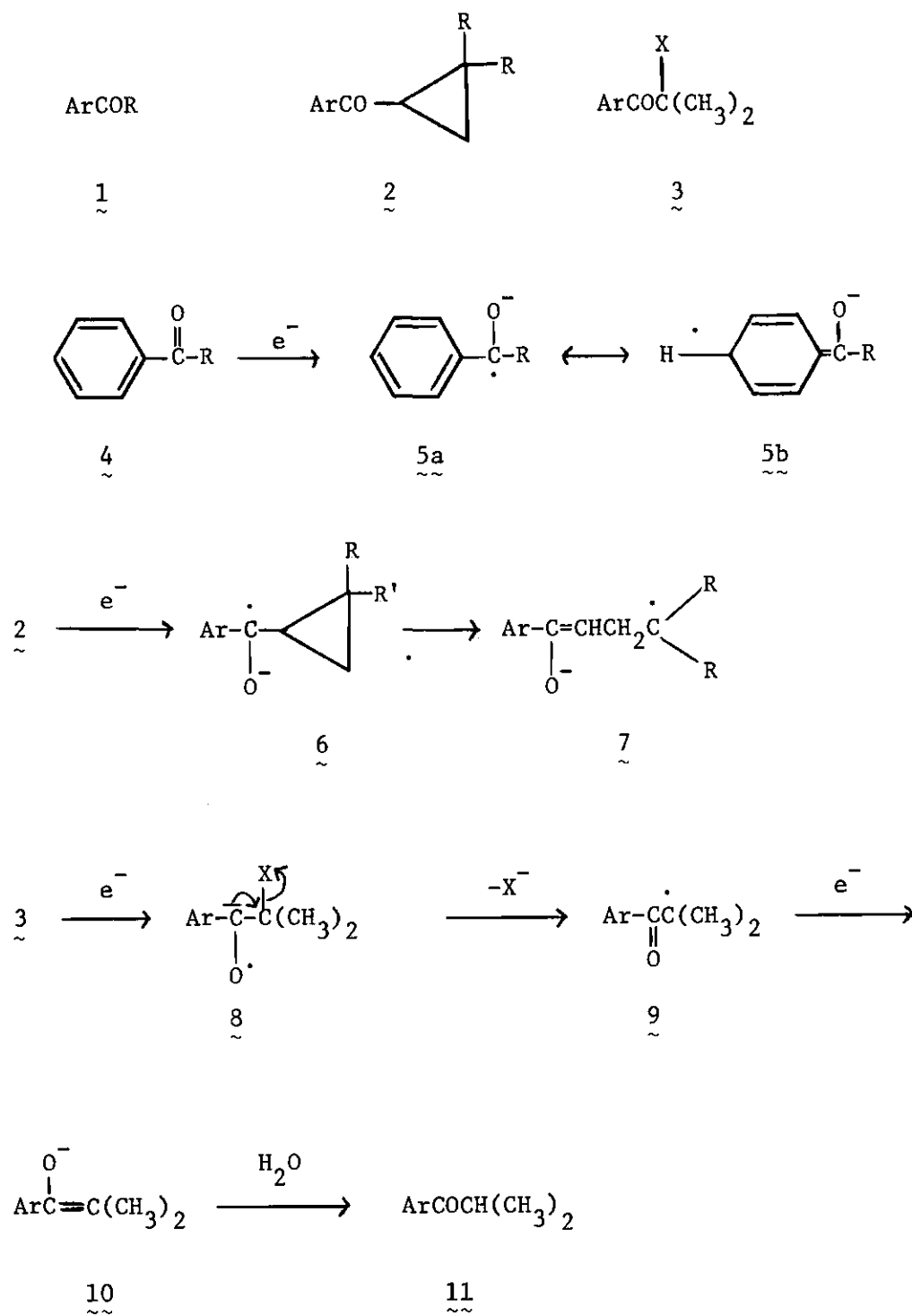
(Scheme I). Reaction of ketones of type 1 (e.g. 4) by an electron-transfer process would yield anion radicals 5 in which spin density would be distributed between the carbonyl carbon atom (5a) and various positions of the aromatic ring (e.g. 5b).<sup>3</sup> Thus, further reaction of such an intermediate could introduce a methyl substituent either at the carbonyl carbon atom or at one of the positions in the aromatic ring.<sup>4</sup>

Reaction of  $\text{Me}_2\text{CuLi}$  with an aryl cyclopropyl ketone 2 offered the possibility that an intermediate anion radical 6 might rearrange to the structurally isomeric ion radical 7 prior to further reaction. Provided that this rearrangement occurred within a time period of  $10^{-3}$  sec or less,<sup>1b,5</sup> rearranged addition products derived from ion radical 7 might be expected. Compounds of the type 3, where X is a group that can be lost as a relatively stable anion, offered the possibility that an intermediate anion radical might eliminate an anion  $\text{X}^-$  provided that this elimination would occur within time periods of the order of  $10^{-3}$  sec or less. The elimination of  $\text{X}^-$  would yield an easily reduced radical 9 that would be expected to react with additional  $\text{Me}_2\text{CuLi}$  to form the enolate 10 and finally the reduction product 11.<sup>1,6</sup>

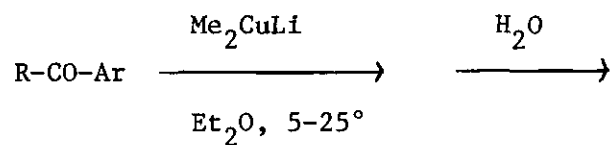
The work contained in this section is a portion of the complete study<sup>7</sup> with the objectives outlined above.

Ketone 13 (Scheme II) was studied as one of the examples of aryl alkyl ketones of type 1. This non-enolizable ketone underwent a relatively slow reaction with  $\text{Me}_2\text{CuLi}$  to form the 1,2-adduct 16. Minor components detected in the reaction mixture were the unchanged

Scheme I



## Scheme II

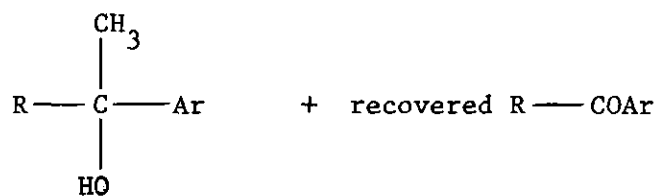


12, R = CH<sub>3</sub>, Ar = Ph (E<sub>1/2</sub> - 2.05V)

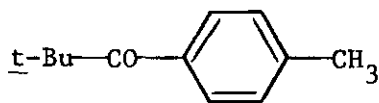
13, R = t-Bu, Ar = Ph (E<sub>1/2</sub> - 2.14V)

14, R = t-Bu, Ar = β-naphthyl (E<sub>1/2</sub> - 1.96V)

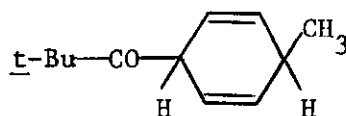
15, R = t-Bu, Ar = α-naphthyl (E<sub>1/2</sub> - 2.03V)



16, R = t-Bu, Ar = Ph (72% yield)



17



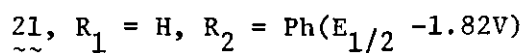
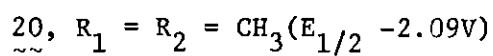
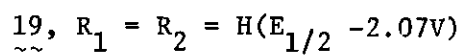
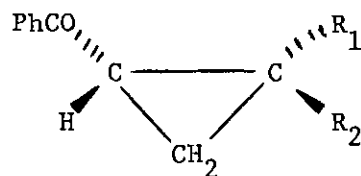
18

ketone 13, and an olefinic product derived from dehydration of the alcohol 16. Examination of these minor compounds by mass spectrometry gave no indication that ring-methylated products, such as 17 or 18 from ketone 13, were present. Consequently, we conclude that if an anion radical of the type 5 is an intermediate in this reaction, recombination with the cluster  $[\text{Me}_4\text{Cu}_2\text{Li}_2]^{\cdot+}$  occurs only at the carbonyl carbon atom (structure 5a) that appears to be the site of highest spin density in this intermediate. It should be noted that each of the ketones 12-15 has a reduction potential (see Scheme I and Table III B-1) within the range (less negative than -2.2V) where electron transfer from  $\text{Me}_2\text{CuLi}$  is feasible. Furthermore, the anion radicals formed from these ketones 12-15 are relatively stable with half-lives greater than 0.1 sec (see Table III B-1).

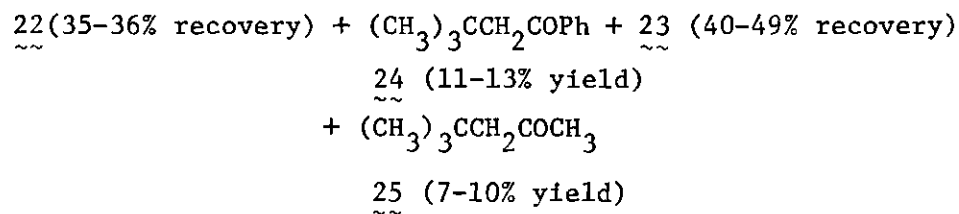
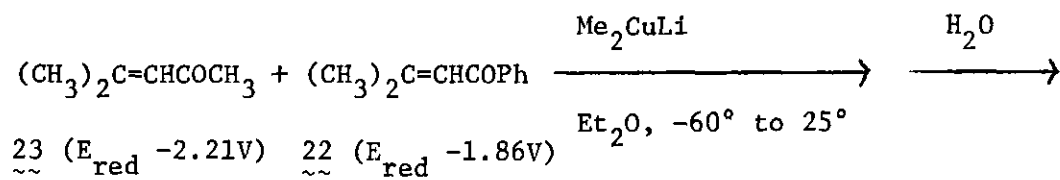
The reduction potentials (Scheme III and Table III B-1) of each of the ketones 19-21 (representative aryl cyclopropyl ketones 2) lie in the range -1.8 to -2.1V. The anion radicals 6 formed from ketones 19 and 20 are relatively stable with half-lives of 4-5 sec (Table III B-1) but the half-life of the anion radical from ketone 21 is much less ( $< 10^{-2}$  sec).<sup>8</sup>

Finally, as part of this same study,<sup>7</sup> the competition experiment summarized in Scheme III was performed to obtain an estimate of the relative rate at which  $\text{Me}_2\text{CuLi}$  reacts with typical enones having different reduction potentials. In conjugate additions of  $\text{Me}_2\text{CuLi}$  to enones the relative reaction rates appear not to be directly related to  $E_{\text{red}}$  values. Thus, the relative rates of

Scheme III



Competition Experiment in Which the Ketone Reactant  
is Present in Excess



conjugate addition of  $\text{Me}_2\text{CuLi}$  to the two enones 22 and 23 were similar although the  $E_{\text{red}}$  values differ by 0.35V. Although experimental difficulties in this competition experiment (see Experimental Section) created some ambiguity in our results, the reaction of  $\text{Me}_2\text{CuLi}$  with the more easily reduced enone 22 does appear to be slightly faster than the reaction with enone 23.

### Experimental Section<sup>9</sup>

#### Preparation or Purification of the Starting Materials

All anhydrous ethereal solvents were freshly distilled from  $\text{LiAlH}_4$ , commercial  $\text{Et}_2\text{O}$  solutions of  $\text{MeLi}$  (halide free, Foote Mineral Co.) were standardized by a double titration procedure,<sup>10</sup> and the colorless, crystalline complex,  $\text{Me}_2\text{SCuBr}$ , was prepared from commercial  $\text{CuBr}$  (Fisher Scientific) as previously described.<sup>1c</sup> A commercial sample of ketone 12 was purified by distillation and the ketone 13 was obtained from  $\text{PhCOCl}$  by a literature procedure.<sup>11</sup>

#### Electrochemical Measurements

The polarographic and cyclic voltammetry measurements employed a custom-made polarographic module, utilizing solid-state amplifiers, that followed the typical three-electrode design. Descriptions of the cells, working electrodes, reference electrodes, and reagent purification procedures have been published previously.<sup>12</sup> In all cases the solvent was anhydrous DMF containing 0.5 M  $n\text{-Bu}_4\text{N}^+\text{BF}_4^-$  as the supporting electrolyte. Previously described procedures<sup>12b,13</sup> were used to estimate the  $E_{1/2}$  values and half-lives



from cyclic voltammetry measurements. The results of these measurements are summarized in Table III B-1.

#### Reactions with $\text{Me}_2\text{CuLi}$

A. Ketone 13. To a solution of  $\text{Me}_2\text{CuLi}$ , prepared by adding 10.1 ml of an  $\text{Et}_2\text{O}$  solution containing 18 mmol of  $\text{MeLi}$  to a solution of 1.77 g (8.6 mmol) of  $\text{Me}_2\text{SCuBr}$  in 12 ml of  $\text{Et}_2\text{O}$  and 9 ml of  $\text{Me}_2\text{S}$ , was added 1.00 g (6.2 mmol) of the ketone 13 in 2 ml of  $\text{Et}_2\text{O}$ . The resulting solution, from which yellow  $(\text{MeCu})_n$  began to precipitate within 5 min, was stirred at  $27^\circ$  for 1 hr and then partitioned between  $\text{Et}_2\text{O}$  and an aqueous solution of  $\text{NH}_4\text{Cl}$  and  $\text{NH}_3$ . The ethereal layer was dried and concentrated to leave 966 mg of crude liquid product. After an aliquot of the product had been mixed with a known weight of internal standard ( $n\text{-C}_8\text{H}_{17}\text{Ph}$ ), glpc analysis (Silicone SE-30 on Chromosorb P) indicated the presence of the unchanged ketone 13 (ret. time 4.5 min, 10% recovery), the alcohol 16 (6.5 min, 72% yield), and  $n\text{-C}_8\text{H}_{17}\text{Ph}$  (10.4 min). The mixture of the ketone 13 ( $R_f$  0.48) and the alcohol 16 ( $R_f$  0.34) was separated by preparative tlc [silica gel with an  $\text{Et}_2\text{O}$ -pentane (1:19 v/v) eluent] and the alcohol fraction was distilled under reduced pressure in a short-path still to separate the alcohol 16 as a colorless liquid, bp  $140\text{--}141^\circ$  (18 mm),  $n_D^{25}$  1.5123 [ $n_D^{14}$  bp  $116\text{--}117^\circ$  (15 mm),  $n_D^{25}$  1.5135]; ir ( $\text{CCl}_4$ ),  $3590\text{ cm}^{-1}$  (OH); uv (95% EtOH), series of weak maxima ( $\epsilon$  125-204) in the region 247-254 m $\mu$ ; nmr ( $\text{CCl}_4$ ),  $\delta$  6.9-7.5 (5H, m, aryl CH), 1.4-1.6 (4H, OH and  $\text{CH}_3$  singlet at 1.52), and 0.88 (9H, s,  $t\text{-Bu}$ ); mass spectrum,

Table III B-1. Electrochemical Reduction of Ketones at 25° in  
DMF Solution Containing 0.5 M  $n\text{-Bu}_4\text{NBF}_4$

Ketone (concn, M $\times 10^3$ )	Polarography			Cyclic Voltammetry	
	$E_{1/2}$ , V vs sce	n	$i_d$ , $\mu\text{a}$	$E_{1/2}$ , V vs sce	Half-life, sec.
12 (6.3) ~~	-2.05	1.1	17-18	-2.12	0.2
13 (5.6 - 5.8) ~~	-2.14 -2.82	1.0 <u>ca.</u> 2	17-25 23	-2.15	3
14 (2.9 - 3.1) ~~	-1.96 -2.44	1.0 1.1	8-11 6-7	-1.95 --a	>10 --a
15 (3.8 - 4.8) ~~	-2.03 -2.41	1.1 1.0	14-18 4	-2.04 --a	3 --a
19 (3.6 - 6.6) ~~	-2.07 -2.73	1.1 1.4	15-18 12	-2.08	<u>ca.</u> 5
20 (2.6 - 4.3) ~~	-2.09	1.1	9-16	-2.09	4
21 (1.8 - 4.2) ~~	-1.82	0.8	8-23	-1.85	$<10^{-2}$
22 (6.4 - 7.0) ~~	-1.86	0.9	11-25	-1.89	0.7
23 (8.0 - 10.2) ~~	-2.21	0.9	15-26	-2.26	0.07

<sup>a</sup>Value not determined.

m/e (rel. intensity) 160 ( $M^+ - H_2O$ , 16), 145 (49), 121 (100), 105 (42), 91 (20), 77 (35), 57 (21), 51 (21), 43 (65), and 41 (20).

Anal. Calcd for  $C_{12}H_{18}O$ : C, 80.85; H, 10.18. Found: C, 80.83; H, 10.18.

Reaction of 969 mg (5.98 mmol) of the ketone 13 with 6.58 mmol of MeLi in 24 ml of  $Et_2O$  afforded 1.02 g (96%) of the alcohol 16,  $n_D^{25}$  1.5145, that was identified with the previously described sample by comparison of ir and nmr spectra.

The ketone fraction from the preparative tlc separation was identified as ketone 13 by comparison of ir and mass spectra. The absence of peaks in the mass spectrum at m/e values larger than 162 (e.g. 176 and 178) indicated the absence of ketone products in which a  $CH_3$  group had been added to the aromatic ring.

#### Competition Experiment with $Me_2CuLi$

Ketones 22 and 23. After a solution of  $Me_2CuLi$ , prepared at 4° from 216 mg (1.05 mmol) of  $Me_2SCuBr$  in 1.5 ml of  $Me_2S$  and 2 ml of  $Et_2O$  and 2.04 mmol of MeLi in 3 ml of  $Et_2O$ , had been cooled to -70°, the solution was maintained at -60 to -70°<sup>15</sup> while a solution of 324 mg (2.03 mmol) of ketone 22 and 201 mg (2.05 mmol) of ketone 23 in 2 ml of  $Et_2O$  was added, dropwise, with stirring. After the resulting orange-colored mixture had been stirred at -70° for 10 min, it was warmed to 4° during approximately 5 min. During this warming, the orange color faded and a yellow precipitate of  $(MeCu)_n$  separated as the solution was warmed above -30°. The reaction mixture was stirred at 4° for 25 min and at 27° for 20 min and then subjected to the usual isolation procedure.

Aliquots of the crude product were mixed with known amounts of an internal standard (tetralin or  $n\text{-C}_{12}\text{H}_{26}$ ) for glpc analysis Carbowax 20M on Porosil). Analysis (glpc) at  $85^\circ$  indicated the presence of ketone 25 (ret. time 3.9 min, 10% yield), ketone 23 (6.9 min, 49% recovery), and  $n\text{-C}_{12}\text{H}_{26}$  (12.6 min). Analysis (glpc) at  $170^\circ$  indicated the presence of tetralin (ret. time 5.7 min), ketone 24 (14.2 min, 11% yield), and ketone 22 (26.2 min, 36% recovery). Collected (glpc) samples of ketones 22, 23, 24, and 25 were identified with authentic samples by comparison of glpc retention times and mass spectra.

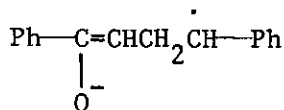
Repetition of this experiment resulted in the following yields of products or reactants: 22, 35%; 23, 40%; 24, 13%; and 25, 7.4%. These consistently low yields (or recoveries) of products and reactants indicated that portions of these materials were being converted to higher molecular weight materials that were not eluted in our glpc analysis. This is presumably the result of Michael and/or aldol condensation of the product enolate anions with the excess enones present in the reaction mixture. In an effort to minimize this problem, a series of comparable reactions were performed in which the mixtures were quenched after shorter reaction times at lower reaction temperatures. In an experiment in which a cold reaction solution was warmed to  $-30^\circ$ , stirred at  $-30^\circ$  for 30 min, and then quenched, the yields were 93% of 22, 86% of 23, 6% of 24, and 0.9% of 25. When the reaction solution was warmed from  $-70^\circ$  to  $-20^\circ$  during 10 min and then quenched immediately, the yields were 96% of 22, 86% of 23, 3.8% of 24, and

1.4% of 25. When the cold ( $-70^{\circ}$ ) reaction solution was warmed to  $-10^{\circ}$  during 10 min, stirred at  $-10^{\circ}$  for 10 min, and then quenched, the yields were 97% of 22, 79% of 23, 3% of 24, and 0.7% of 25. Thus, it appears that the reaction of the more easily reduced enone 22 with  $\text{Me}_2\text{CuLi}$  is slightly more rapid than the corresponding reaction with the enone 23.

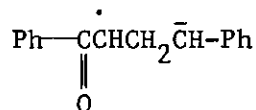
### References and Notes

1. (a) H. O. House and M. J. Umen, J. Org. Chem., **38**, 3893 (1973); J. Amer. Chem. Soc., **94**, 5495 (1972); (b) H. O. House and P. D. Weeks, ibid., **97**, 2770, 2778, 2785 (1975); (c) H. O. House, C. -Y. Chu, J. M. Wilkins, and M. J. Umen, J. Org. Chem., **40**, 1460 (1975); (d) For a brief review, see H. O. House, Accts. Chem. Res., **9**, 59 (1976).
2. For an extensive survey of electrode potentials, see H. Siegerman in "Technique of Electroorganic Synthesis," Part II, N. L. Weinberg, Ed., Wiley-Interscience, New York, N. Y., 1975, pp. 667-1056.
3. The hyperfine coupling constants observed in the epr spectra of benzaldehyde and acetophenone anion radicals suggest that about one-third of the spin density is centered at the carbonyl carbon atom with the remainder being distributed among the o, m, and p-positions of the benzene ring; P. B. Ayscough, "Electron Spin Resonance in Chemistry," Methuen and Co., Ltd., London, 1967, pp. 274-279.
4. One apparent example of this possibility is the reaction of various benzophenone derivatives with t-BuMgCl to form both products with the t-Bu group bound to the carbonyl carbon atom and dihydroaromatic products with the t-Bu group at the o- or p-position of the dihydroaromatic ring. T. Holm and I. Crossland, Acta Chem. Scand., **25**, 59 (1971).
5. (a) H. O. House and K. A. J. Snoble, J. Org. Chem., **41**, 3076 (1976); (b) J. A. Marshall and R. A. Ruden, ibid., **37**, 659 (1972).
6. For examples of this type of reaction sequence with enones, see (a) D. J. Hannah and R. A. J. Smith, Tetrahedron Lett., No. 3, 187 (1975); (b) A. Nilsson and A. Ronl  n, ibid., No. 13, 1107 (1975); (c) R. A. Ruden and W. E. Litterer, ibid., No. 25, 2043 (1975).
7. H. O. House, A. V. Prabhu, J. M. Wilkins, and L. F. Lee, J. Org. Chem., **41**, 3067 (1976).

8. The substantial decrease in the stability of the ketyl 6 with a phenyl substituent (from ketone 21) when compared with the analogous ketyl with two methyl substituents (from ketone 20) presumably reflects the fact that the phenyl substituent can stabilize both radical and carbanionic structures i and ii.



i



ii

H. Shiota, K. Ohkata, and T. Hanafusa [Chem. Lett., 1153 (1974)] have reported that exhaustive reduction of ketones 19 and 20 with Na in NH<sub>3</sub> yielded alkylated cyclopropanes whereas the comparable reduction of ketone 21 yielded 1,4-diphenylbutane. Although the latter result could be regarded as an example of the ion radical rearrangement 6 → 7, the facts that ketone 21 reacts with Me<sub>2</sub>CuLi without appreciable ring opening and that anion radical intermediates appear to have longer life times in cuprate reactions than in metal-NH<sub>3</sub> reductions (Ref. 1b, d) leads us to believe that this ring opening occurred after initial reduction of the carbonyl group.

9. All melting points are corrected and all boiling points are uncorrected. Unless otherwise stated MgSO<sub>4</sub> was employed as a drying agent. The ir spectra were determined with a Perkin Elmer, Model 257, infrared recording spectrophotometer fitted with a grating. The uv spectra were determined with a Cary, Model 14, or a Perkin Elmer, Model 202, recording spectrophotometer. The proton nmr spectra were determined at 60 MHz with a Varian, Model A-60 or Model T-60-A, nmr spectrometer and the <sup>13</sup>C nmr spectra were determined at 100 MHz with a JEOL Fourier transform spectrometer, Model PFT-100. The chemical shift values are expressed in δ values (ppm) relative to a Me<sub>4</sub>Si internal standard. The mass spectra were obtained with an Hitachi (Perkin Elmer), Model RMU-7, or a Varian, Model M-66, mass spectrometer. All reactions involving strong bases or reactive organometallic intermediates were performed under a nitrogen atmosphere.

10. G. M. Whitesides, C. P. Casey, and J. K. Krieger, J. Amer. Chem. Soc., 93, 1379 (1971).
11. (a) G. H. Posner, C. E. Whitten, and J. J. Sterling, J. Amer. Chem. Soc., 95, 7788 (1973); (b) G. H. Posner and C. E. Whitten, Org. Syn., 55, 122 (1975).
12. (a) H. O. House and E. F. Kinloch, J. Org. Chem., 39, 1173 (1974); (b) H. O. House, D. Koepsell, and W. Jaeger, ibid., 38, 1167 (1973).
13. (a) K. W. Bowers, R. W. Giese, J. Grimshaw, H. O. House, N. H. Kolodny, K. Kornberger, and D. K. Roe, J. Amer. Chem. Soc., 92, 2783 (1970); (b) R. N. Adams, "Electrochemistry at Solid Electrodes," Marcel Dekker, Inc., New York, N. Y., 1969, pp. 143-158.
14. Ramart-Lucas, Ann. Chim. (Paris), [8] 30, 353 (1913).
15. Since neither of the ketones used reacts with  $\text{Me}_2\text{CuLi}$  at  $-60^\circ$ , this procedure was followed to insure complete mixing of the cuprate and the ketones before any reaction occurred.



PART C. A CONVENIENT PRECURSOR FOR THE GENERATION  
OF LITHIUM ORGANOCUPRATES

Introduction and Discussion

From various studies of the preparation and use of lithium organocuprate reagents,<sup>1</sup> it has become apparent that two practical problems complicating the general use of these reagents are inadvertent thermal decomposition<sup>2</sup> and inadvertent oxidation leading to coupling of the organic residues.<sup>3</sup> Both of these initial side reactions often lead to the formation of Cu(0) which usually appears as a black colloidal suspension in the reaction mixture and is believed to catalyze the decomposition of still more copper reagent.<sup>4</sup>

The most common preparative procedure for lithium dialkylcuprates consists of addition of 2 mol equiv of an alkyllithium solution to an ethereal slurry of one of the commercially available Cu(I) salts, CuI, CuBr, or CuCl. As noted previously,<sup>5</sup> use of this procedure may be accompanied by partial decomposition, especially if the reagent is one of the relatively thermally unstable cuprates, such as a vinyl derivative or a derivative with alkyl substituents that have  $\beta$  H atoms. Among the causes of this decomposition are the presence of other transition metal impurities in the commercial Cu(I) salts and the occurrence of local overheating during the exothermic reaction of alkyl-lithium with insoluble Cu(I) salts.<sup>5</sup> Another cause of decomposition

is the presence of significant amounts of Cu(II) salts, which are effective oxidants for cuprates,<sup>3,5b</sup> in many commercial samples of Cu(I) halides. Other Cu(I) compounds that have been used to form cuprate reagents include the insoluble derivatives CuCN<sup>6</sup> and  $n\text{-C}_3\text{H}_7\text{C}\equiv\text{CCu}$ <sup>7</sup> and the more soluble derivatives  $t\text{-BuOCu}$ ,<sup>8</sup>  $\text{PhSCu}$ ,<sup>8</sup> and  $t\text{-BuC}\equiv\text{CCu}$ .<sup>5a</sup> The latter, soluble Cu(I) acetylide offers the advantage of being a scavenger for oxidizing agents such as Cu(II) salts, undergoing oxidation to form the volatile diyne,  $t\text{-BuC}\equiv\text{CC}\equiv\text{CBu-}t$ .<sup>5</sup> Unfortunately, the advantages of ether solubility and "protection" from oxidants offered by  $t\text{-BuC}\equiv\text{CCu}$  are offset by the fact that the precursor,  $t\text{-BuC}\equiv\text{CH}$ , is not presently available commercially at a reasonable cost. This fact has led us to examine other possible Cu(I) derivatives that might offer the advantages of both ether solubility and easy purification to separate unwanted Cu(II) impurities. In earlier work,<sup>5,9</sup> we have noted the solubility advantages offered by several Cu(I) halide complexes such as  $n\text{-Bu}_3\text{PCuI}$ ,  $(\text{MeO})_3\text{PCuI}$ ,  $(\text{MeO})_3\text{PCuBr}$ , and especially, the liquid complexes  $(n\text{-Bu}_2\text{S})_2\text{CuI}$  and  $(n\text{-Bu}_2\text{S})_2\text{CuBr}$ . The use of these complexes in synthetic work is made less attractive by the relatively high boiling points of the ligands,  $n\text{-Bu}_2\text{S}$  (bp 189°),  $n\text{-Bu}_3\text{P}$  [bp 150° (50 mm)], and  $(\text{MeO})_3\text{P}$  (bp 112°) that complicate their removal from reaction products and by the persistent disagreeable odor associated with phosphine and phosphite ligands. We were attracted by reports indicating that complexes of certain Cu(I) salts with the ligand  $\text{Me}_2\text{S}$  (bp 37°) were both soluble in ether<sup>10</sup> and could be obtained as crystalline solids.<sup>11</sup> Upon exploring

the reaction of  $\text{Me}_2\text{S}$  with Cu(I) halides, we found that each of the 1:1 complexes  $\underline{1}$ ,  $\underline{2}$ , and  $\underline{3}$  (Scheme I) could easily be obtained as a colorless crystalline solid that was readily separated from Cu(II) contaminants. Since Cu(II) salts form solutions of highly colored complexes with  $\text{Me}_2\text{S}$  (dark green solution with  $\text{CuCl}_2$  and dark red solution with  $\text{CuBr}_2$ ), the absence of these Cu(II) impurities in the colorless Cu(I) complexes is readily discerned. Although the iodide complex  $\underline{3}$  spontaneously lost  $\text{Me}_2\text{S}$  on standing, the bromide complex  $\underline{2}$  proved to be both convenient to prepare in pure form and stable to storage. Thus, by conversion to the complex  $\underline{2}$ , commercial samples of CuBr are readily purified to remove Cu(II) salts and other impurities.

Although none of the complexes  $\underline{1}$  -  $\underline{3}$  was soluble in ether, solutions were readily obtained when additional  $\text{Me}_2\text{S}$  was added. The bromide complex  $\underline{2}$  could be dissolved in  $\text{Et}_2\text{O}$ , PhH, or  $\text{CHCl}_3$  when  $\text{Me}_2\text{S}$  was added suggesting the reversible formation of complexes such as  $(\text{Me}_2\text{S})_2\text{CuBr}$  or  $(\text{Me}_2\text{S})_3\text{CuBr}$  in these solutions. Treatment of solutions of the complex  $\underline{2}$  in  $\text{Et}_2\text{O}$ - $\text{Me}_2\text{S}$  with 2 mol equiv of either MeLi (at 0-10°) or  $\text{CH}_2=\text{CHLi}$  (at -40 to -50°) produced solutions of the corresponding cuprate reagents,  $\text{Me}_2\text{CuLi}$  and  $(\text{CH}_2=\text{CH})_2\text{CuLi}$ .

The experimental work described in this section is part of a more general examination<sup>12</sup> of various preparative procedures for lithium organocuprates. One contribution in this area involved examining the use of various cuprate preparations for the conjugate addition of a vinyl group to the unsaturated ketone  $\underline{6}$ .



Reaction of the enone 6 (Scheme II) with  $(\text{CH}_2=\text{CH})$  ( $\text{t-BuC}\equiv\text{C}$ ) $\text{CuLi}^5$  or with  $(\text{CH}_2=\text{CH})_2\text{CuLi}$  (from a solution of  $\text{Me}_2\text{SCuBr}$ ) formed a mixture of stereoisomeric adducts 7 - 9 in yields of 88% and 86%, respectively. The product mixture contained ca. 80% of the ketone 7, ca. 15% of the epimeric ketone 8, and ca. 5% of the stereoisomeric ketones 9 with equatorial vinyl substituents. Thus, the conjugate addition of a vinyl group, like the previously described<sup>5</sup> conjugate addition of a methyl group, to the enone 6, occurs predominantly from the direction that introduces an axial substituent.

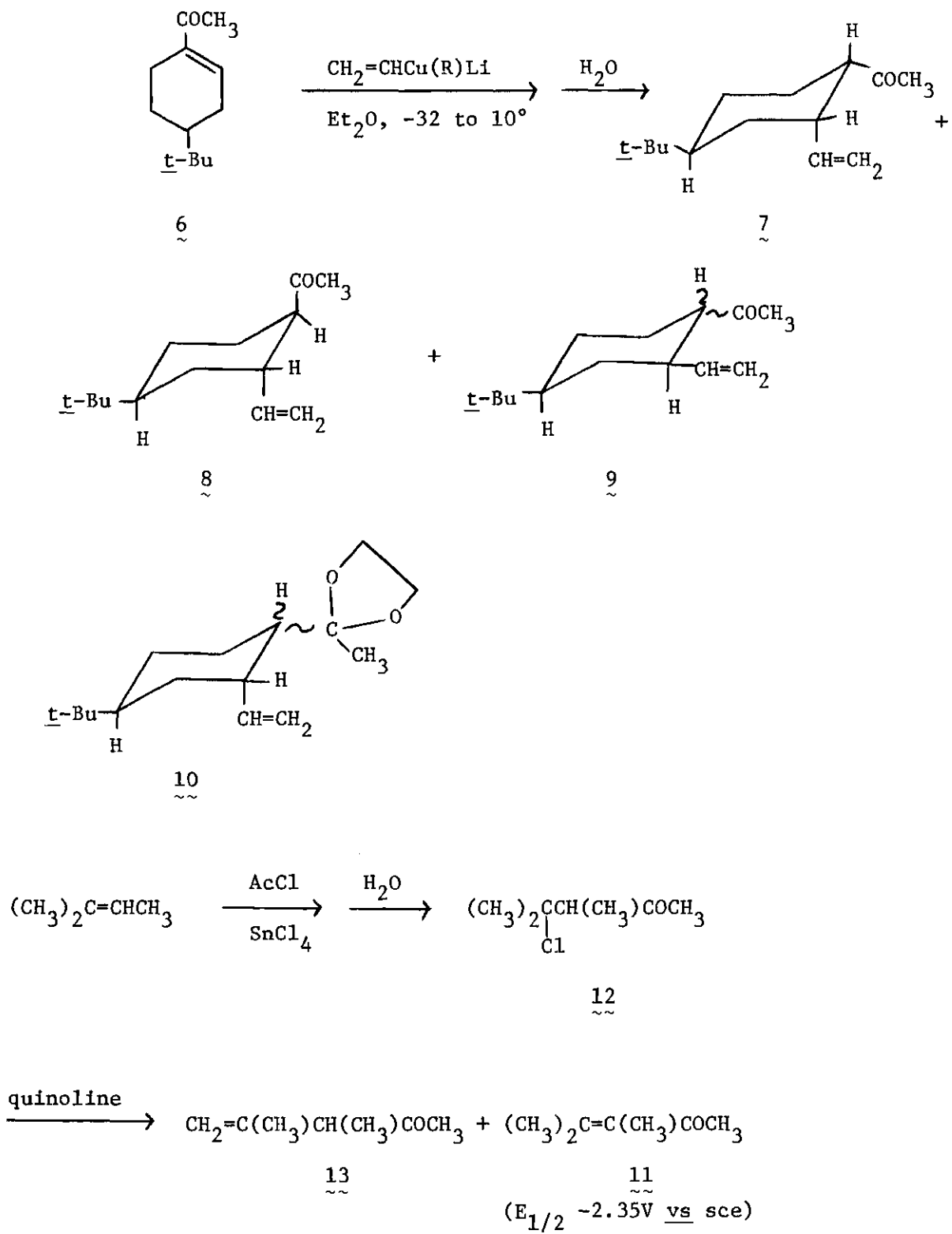
To probe the question of relative reactivities of vinyl and methyl groups in a mixed cuprate, we synthesized (Scheme II) the trisubstituted enone 11 that was expected<sup>14</sup> to have a sufficiently negative reduction potential that its reaction with  $\text{Me}_2\text{CuLi}$  would be questionable.<sup>5a</sup> This enone 11 was prepared by the acetylation of 2-methyl-2-butene.<sup>15</sup>

### Experimental Section<sup>16</sup>

#### Preparation of Starting Materials

Previously described procedures were used to prepare t-butylacetylene<sup>5</sup> and to convert<sup>5,17</sup> 4-t-butylcyclohexanone to its crude cyanohydrin (a mixture of epimers); the bulk of the material melted at 53-55° with a small amount of remaining material that melted at 63-65°. A mixture of 197.1 g (1.089 mol) of this cyanohydrin, 180 g of  $\text{Ac}_2\text{O}$ , and 12 ml of  $\text{AcCl}$  was refluxed for 5 hr at which time tlc analysis (silica gel coating,  $\text{CH}_2\text{Cl}_2$ - $\text{Et}_2\text{O}$

Scheme II



mixture as eluent) indicated complete conversion of the cyanohydrin ( $R_f$  0.22) to its acetate 4 ( $R_f$  0.62). A small portion of the crude reaction mixture was partitioned between  $\text{Et}_2\text{O}$  and aqueous  $\text{NaCl}$  and the  $\text{Et}_2\text{O}$  solution was washed successively with aqueous  $\text{NaHCO}_3$  and  $\text{H}_2\text{O}$  and then dried and concentrated. The crude acetate 4, which crystallized on standing, exhibited glpc peaks (silicone SE-52 on Chromosorb P) corresponding to 4-t-butylcyclohexanone (ret. time 3.9 min., ca. 2%) and the acetate 4 (19.2 min, ca. 98%). The bulk of the crude acetate 4 in  $\text{Ac}_2\text{O}$  solution was added dropwise to a tube packed with glass beads and heated to  $550\text{--}570^\circ$ .<sup>18</sup> A slow stream of  $\text{N}_2$  was used to sweep the products into a cooled flask. The crude pyrolysis mixture contained (glpc, silicone SE-30 on Chromosorb P) primarily the unsaturated nitrile 5b (ret. time 7.8 min) accompanied by small amounts of 4-t-butylcyclohexanone (4.2 min) and the unchanged acetate 4 (10.9 min) as well as  $\text{HOAc}$  and  $\text{Ac}_2\text{O}$ . After the bulk of the  $\text{HOAc}$  had been removed by distillation ( $42\text{--}46^\circ$  at 73 mm), the residue was partitioned between  $\text{Et}_2\text{O}$  and aqueous  $\text{NaCl}$  and the  $\text{Et}_2\text{O}$  solution was washed with aqueous  $\text{NaHCO}_3$ , dried, and concentrated. The residual unsaturated nitrile, a brown solid, was recrystallized from  $\text{EtOH}$  to separate 108 g (61%) of the nitrile 5 as white plates, mp  $45\text{--}46^\circ$  (lit.<sup>17</sup> mp  $45\text{--}46^\circ$ ), with ir and nmr spectra corresponding to those previously reported.<sup>5</sup> Reaction of the nitrile 5 with ethereal  $\text{MeLi}$ <sup>5</sup> yielded 65% of the ketone 6, bp  $67\text{--}81^\circ$  (0.14 mm),  $n_D^{25}$  1.4838–1.4842 [lit.<sup>5</sup>  $141\text{--}143^\circ$  (19 mm),  $n_D^{25}$  1.4844], that exhibited a single glpc peak (ret. time 12.8 min) on a column (silicone SE-30 on

Chromosorb P) where the retention time of the starting nitrile 5 was 9.4 min. The ir and nmr spectra of the product 6 corresponded to those previously reported.<sup>5</sup>

Commercial Et<sub>2</sub>O solutions containing about 1.6 M MeLi (halide free, Foote Mineral Co.) and THF solutions containing 1.6-2.1 M CH<sub>2</sub>=CHLi (Lithium Corporation of America) were standardized by a double titration procedure<sup>19</sup> in which aliquots of the reagent, both before and after reaction with 1,2-dibromoethane, were titrated with standard aqueous acid. All of the commercial THF solutions of CH<sub>2</sub>=CHLi (Lithium Corporation of America) were contaminated with substantial amounts of mineral oil (presumably from the Li dispersion used) that contaminated the final product and had to be separated by fractional distillation. Commercial CuI (Fisher Scientific) was purified by solution in aqueous KI and reprecipitation.<sup>20</sup>

#### Preparation of the Vinyl Ketones 7 and 8

To a cold (0°) solution of 0.139 mol of MeLi in 80 ml of Et<sub>2</sub>O was added 11.6 g (0.142 mol) of t-BuC≡CH. The resulting solution of t-BuC≡CLi was added to a cold (5°) slurry of 26.5 g (0.139 mol) of purified<sup>20</sup> CuI in 160 ml of Et<sub>2</sub>O and the resulting mixture was warmed to 29° with stirring during 15 min to give a red-orange solution of t-BuC≡CCu. This solution was cooled to -50° and the resulting orange suspension was treated with a solution of 0.129 mol of CH<sub>2</sub>=CHLi<sup>22</sup> in 68 ml of Et<sub>2</sub>O while the temperature was maintained at -45 to -50°. The resulting solution, whose color changed progressively from orange to red to green, was warmed to -32° with stirring during 10 min and then treated with a



solution of 7.2 g (40 mmol) of the ketone 6 in 80 ml of Et<sub>2</sub>O. The resulting mixture was stirred at 0 - 10° for 1 hr and then added to 150 ml of ethanolic 1 M HOAc. The resulting mixture was neutralized with aqueous NaHCO<sub>3</sub> and extracted with Et<sub>2</sub>O. After the Et<sub>2</sub>O extract had been washed successively with aqueous 28% NH<sub>3</sub><sup>21</sup> and with H<sub>2</sub>O, it was dried and concentrated to leave 7.94 g of liquid containing (glpc, silicone fluid QF<sub>1</sub> on Chromosorb P) a mixture of a component believed to be one epimer of ketone 9 (ret. time 10.1 min, ca. 4%), ketone 8 (12.8 min, ca. 15%), a component believed to be the second epimer of ketone 9 (15.4 min, ca. 3%), and ketone 7 (17.5 min, ca. 78%). A 5.69-g aliquot of this crude product was distilled to separate 4.745 g of fractions, bp 69-91° (0.1-0.7 mm) containing various mixtures of the ketones 7, 8, and 9. A collected (glpc) sample of the major product 7 was obtained as a colorless liquid, n<sub>D</sub><sup>25</sup> 1.4728; ir (CCl<sub>4</sub>), 1710 (C=O), 1635 (C=C), and 920 cm<sup>-1</sup> (CH=CH<sub>2</sub>); uv max (95% EtOH), 278 mμ (ε 35); nmr (CCl<sub>4</sub>), δ 4.8-6.2 (3H, m, vinyl CH), 2.8-3.2 (1H, m, allylic CH), 2.38 [1H, d(J<sub>aa</sub> = 10.8 Hz) of t(J<sub>ae</sub> = 4.4 Hz), axial H of CHCO, exchanged with NaOMe in MeOD], 1.99 (3H, s, CH<sub>3</sub>CO, exchanged with NaOMe in MeOD), 0.9-1.9 (7H, m, aliphatic CH), and 0.85 (9H, s, t-Bu); the signal at δ 2.38 exhibited the same splitting pattern and J values when the spectrum was determined at 100 MHz with a JEOL nmr spectrometer; mass spectrum m/e (relative intensity), 208 (1, M<sup>+</sup>), 152 (8), 151 (6), 109 (17), 58 (30), 57 (30), and 43 (100); calcd for C<sub>14</sub>H<sub>24</sub>O, 208.1827; found, 208.1847.

Anal. calcd for C<sub>14</sub>H<sub>24</sub>O: C, 80.71; H, 11.61. Found:

C, 80.91; H, 11.78.

In a larger scale reaction the mixed cuprate, from 27.0 g (329 mmol) of  $t\text{-BuC}\equiv\text{CH}$ , 329 mmol of MeLi, 62.5 g (329 mmol) of purified CuI, 308 mmol of  $\text{CH}_2=\text{CHLi}$ ,<sup>22</sup> and 773 ml of  $\text{Et}_2\text{O}$ , was treated with a solution of 17.1 g (95 mmol) of the ketone 6 in 150 ml of  $\text{Et}_2\text{O}$ . After following the previously described reaction and isolation procedures, distillation afforded 15.70 g (88%) of colorless liquid product, bp 82-100° (0.4 mm) containing (glpc) the ketones 7 (ca. 80%) and 8 (ca. 11%) as well as two minor components (ca. 2% and 5%) believed to be the epimers of ketone 9 and a minor unidentified component (ca. 2%).

A solution of 15.0 g (73.0 mmol) of  $\text{Me}_2\text{SCuBr}$  (2) in 75 ml of  $\text{Me}_2\text{S}$  and 100 ml of  $\text{Et}_2\text{O}$  was cooled to -50 to -57° (accompanied by partial crystallization of the complex 2) and then 93.2 ml of a THF solution containing 153 mmol of  $\text{CH}_2=\text{CHLi}$  was added, dropwise with stirring. The resulting reddish-brown solution was warmed to -35° and a solution of 12.06 g (67.0 mmol) of the ketone 6 in 50 ml of  $\text{Et}_2\text{O}$  was added dropwise with stirring. The resulting mixture was stirred at -30 to -35° for 10 min and then allowed to warm to 25° with stirring during 1 hr. As the solution warmed from -30 to 25°, it became dark brown to black in color. The reaction mixture was partitioned between ether and aqueous  $\text{NH}_4\text{Cl}$  and  $\text{NH}_3$  and then the ether solution was washed successively with aqueous 10%  $\text{Na}_2\text{S}_2\text{O}_3$  and with aqueous 28%  $\text{NH}_3$ . The organic solution was then decolorized with carbon, dried, and concentrated to leave a pale yellow liquid (59.89 g, containing mineral oil

from the  $\text{CH}_2=\text{CHLi}$ ). The crude mixture contained (glpc, Carbowax 20 M on Chromosorb P) the ketone 7 (ret. time 17.1 min, ca. 80% of the mixture) as well as a partially resolved mixture of ketones 8 and 9 (9.9 min and 12.4 min, ca. 20% of the mixture). A collected (glpc) sample of the major product, ketone 7, was identified with the previously described sample by comparison of glpc retention times and ir and nmr spectra. Distillation of the crude product separated 11.94 g (85.7%) of a mixture of ketones 7, 8, and 9 as fractions of colorless liquid, bp 83-87° (1.5 mm),  $n_D^{25}$  1.4724-1.4730, and left the higher boiling mineral oil (from the  $\text{CH}_2=\text{CHLi}$ ) in the still pot.

#### Preparation of the Ketal 10

A solution of 13.16 g (63.5 mmol) of the previously described mixtures of ketones 7 (ca. 80%) and 8 (ca. 11% plus minor amounts of ketones 9), 306 mg of  $p\text{-TsOH}\cdot\text{H}_2\text{O}$ , and 170 ml of ethylene glycol in 950 ml of PhH was refluxed for 68 hr with continuous separation of  $\text{H}_2\text{O}$  and then partitioned between  $\text{Et}_2\text{O}$  and aqueous  $\text{NaHCO}_3$ . The organic layer was dried and concentrated to leave 16.14 g of the crude ketal 10 as a pale yellow liquid containing (ir analysis) only a very minor amount of the starting ketones 7-9 and containing (glpc, silicone fluid QF<sub>1</sub> on Chromosorb P) two major components, the epimeric ketals 10 [ret. times 13.3 (ca. 20%), and 15.1 min (ca. 80%)]. A collected (glpc) sample of the mixture of epimers 10 was obtained as a colorless liquid,  $n_D^{25}$  1.4790; ir ( $\text{CCl}_4$ ), 1630 (C=C) and  $910\text{ cm}^{-1}$  ( $\text{CH}=\text{CH}_2$ ); uv (95% EtOH), end absorption with  $\epsilon$  66 at 210 m $\mu$ ; nmr ( $\text{CCl}_4$ ),  $\delta$  5.8-6.2 and 4.7-5.2

(3H, m, vinyl CH), 3.7-4.0 (4H, m, CH<sub>2</sub>O), 1.0-3.0 [12H, m, including two singlets at 1.23 (minor) and 1.15 (major), 3H, CH<sub>3</sub> of epimers], and 0.82 (9H, s, t-Bu)]; mass spectrum m/e (relative intensity), 252 (<1, M<sup>+</sup>), 237 (1), 87 (100), and 43 (18).

Anal. Calcd for C<sub>16</sub>H<sub>28</sub>O<sub>2</sub>: C, 76.14; H, 11.18. Found: C, 76.24; H, 11.20.

#### Preparation of the Unsaturated Ketone 11

To a cold (4°) mixture of 20.01 g (285 mmol) of 2-methyl-2-butene and 2.55 g (9.8 mmol) of freshly distilled SnCl<sub>4</sub> (bp 114°) was added, dropwise and with stirring, 26.8 g (341 mmol) of AcCl.<sup>15</sup> After the addition was complete, the yellow reaction solution was allowed to warm to 25° (accompanied by formation of a red-brown color) and then the mixture was stirred at 25-27° for 3.5 hr. After the reaction mixture had been poured onto ice and extracted with Et<sub>2</sub>O, the ethereal solution was washed successively with aqueous NaHCO<sub>3</sub> and with H<sub>2</sub>O and then dried and concentrated. The crude residual liquid was distilled to separate 19.05 g of fractions, bp 43-80° (44 mm), n<sub>D</sub><sup>25</sup> 1.4401 - 1.4449, that contain (ir and nmr analysis) a mixture of the unsaturated ketones 11 and 13 and the chloro-ketone 12. A mixture of this crude product (12.05 g) with 16.53 g (128 mmol) of freshly distilled quinoline [bp 87-91° (0.35 mm)] was heated under reflux (ca. 140°) for 2.5 hr and then cooled and partitioned between Et<sub>2</sub>O and H<sub>2</sub>O. The ethereal layer was dried and concentrated and the residual liquid was distilled to separate 12.15 g (38%) of fractions, bp 73.5-75.5° (20 mm), that contained (glpc, TCEP on Chromosorb P) ca. 12-33% of the unconjugated

ketone 13 (ret. time 4.5 min) and 67-88% of the conjugated ketone 11 (9.1 min). A mixture of these ketones 11 and 13 (12.15 g) and 120 mg of p-TsOH was heated to 140° for 20 min and then cooled and partitioned between Et<sub>2</sub>O and aqueous NaHCO<sub>3</sub>. The ethereal solution was dried and concentrated to leave a ketone mixture containing (glpc) ca. 19% of ketone 13 and ca. 81% of ketone 11.

The mixture was fractionally distilled at atmospheric pressure with 55-cm Teflon spinning-band column to separate the pure ketone 13, bp 125°,  $n_D^{25}$  1.4201, followed by fractions containing (glpc) mixtures of ketones 11 and 13, and finally, the pure ketone 11, bp 146°,  $n_D^{25}$  1.4500 (lit. bp 146°, <sup>23</sup> 149.5°<sup>15</sup>,  $n_D^{24}$  1.4473<sup>13</sup>). The ketone 13 exhibited ir peaks (CCl<sub>4</sub>) at 1718 (C=O), 1641 (C=C), and 890 cm<sup>-1</sup> (C=CH<sub>2</sub>) with nmr peaks (CCl<sub>4</sub>) at 4.7-5.0 (2H, m, vinyl CH), 3.15 (1H, q, J = 7 Hz, allylic CH), 2.01 (3H, s, CH<sub>3</sub>CO), 1.65 (3H, partially resolved multiplet, allylic CH<sub>3</sub>), and 1.10 (3H, d, J = 7 Hz, CH<sub>3</sub>). The ketone 11 has the following spectroscopic properties: ir (CCl<sub>4</sub>), 1684 (conjugated C=O) and 1615 cm<sup>-1</sup> (conjugated C=C); uv max (95% EtOH), 247 mμ (ε 6000); nmr (CCl<sub>4</sub>), δ 2.12 (3H, s, COCH<sub>3</sub>), 1.80 (6H, s, CH<sub>3</sub>), and 1.73 (3H, s, CH<sub>3</sub>); mass spectrum, m/e (rel. intensity), 112 (M<sup>+</sup>, 100), 97 (64), 69 (93), 53 (22), 43 (63), 41 (81), and 39 (30).

### References and Notes

1. For recent reviews, see (a) G. Posner, Org. Reactions., 19, 1 (1972); (b) G. Posner, ibid., 22, in press; (c) H. O. House in Proceedings of the XVII Robert A. Welch Foundation Conference, Houston, Texas, November 5-7, 1973, pp. 101-149.
2. Potential side reactions arising from thermal decomposition to form CuH derivatives are noted elsewhere; see H. O. House and J. C. Dubose, J. Org. Chem., 40, 788 (1975) and references therein.
3. (a) G. M. Whitesides, J. San Filippo, Jr., C. P. Casey, and E. J. Panek, J. Amer. Chem. Soc., 89, 5302 (1967); (b) G. M. Whitesides, W. F. Fischer, Jr., J. San Filippo, Jr., R. W. Bashe, and H. O. House, ibid., 91, 4871 (1969).
4. K. Wada, M. Tamura, and J. Kochi, J. Amer. Chem. Soc., 92, 6656 (1970); M. Tamura and J. Kochi, J. Organometal. Chem., 42, 205 (1972); J. K. Kochi, Accts Chem. Res., 7, 351 (1974).
5. (a) H. O. House and M. J. Umen, J. Org. Chem., 38, 3893 (1973); (b) J. G. Smith and R. T. Wikman, Syn. React. Inorg. Metal-Org. Chem., 4, 239 (1974).
6. J. P. Gorlier, L. Hamon, J. Levisalles, and J. Wagnon, Chem. Commun., No. 3, 88 (1973).
7. E. J. Corey and D. J. Beames, J. Amer. Chem. Soc., 94, 7210 (1972).
8. G. H. Posner and C. E. Whitten, Tetrahedron Lett., No. 21, 1815 (1973); G. H. Posner, C. E. Whitten, and J. J. Sterling, J. Amer. Chem. Soc., 95, 7788 (1973).
9. (a) H. O. House, W. L. Respass, and G. M. Whitesides, J. Org. Chem., 31, 3128 (1966); (b) H. O. House and W. F. Fischer, Jr., ibid., 33, 949 (1968); (c) H. O. House, W. F. Fischer, Jr., M. Gall, T. E. McLaughlin, and N. P. Peet, ibid., 36, 3429 (1971).
10. R. D. Clark and C. H. Heathcock, Tetrahedron Lett., No. 18, 1713 (1974).

11. T. Kamidate, T. Yotsuyanagi, and K. Aomura, Nippon Kagaku Kaishi, No. 11, 2087 (1972); Chem. Abstr., 78, 34498 u (1973).
12. H. O. House, C. -Y. Chu, J. M. Wilkins, and M. J. Umen, J. Org. Chem., 40, 1460 (1975).
13. (a) G. H. Posner, C. E. Whitten, J. J. Sterling, and D. J. Brunelle, Tetrahedron Lett., No. 30, 2591 (1974);  
(b) In studies of other mixed cuprates,  $R(R')CuLi$ , W. H. Mandeville and G. M. Whitesides [J. Org. Chem., 39, 400 (1974)] have found the relative ease of transfer to lie in the order:  $1^\circ$  or  $2^\circ$  alkyl >  $3^\circ$  alkyl > phenyl > alkoxy or alkynyl.
14. H. O. House, L. E. Huber, and M. J. Umen, J. Amer. Chem. Soc., 94, 8471 (1972).
15. The general procedure of F. H. Cottee, B. P. Straughan, C. J. Timmons, W. F. Forbes, and R. Shilton, J. Chem. Soc., B, 1146 (1967).
16. All melting points are corrected and all boiling points are uncorrected. Unless otherwise stated  $MgSO_4$  was employed as a drying agent. The ir spectra were determined with a Perkin Elmer, Model 257, infrared recording spectrophotometer fitted with a grating. The uv spectra were determined with a Cary, Model 14, or a Perkin Elmer, Model 202, recording spectrophotometer. The proton nmr spectra were determined at 60 MHz with a Varian, Model A-60 or Model T-60A, nmr spectrometer and the  $^{13}C$  nmr spectra were determined at 100 MHz with a JEOL Fourier transform spectrometer, Model PFT-100. The chemical shift values are expressed in  $\delta$  values (ppm) relative to a  $Me_4Si$  internal standard. The mass spectra were obtained with an Hitachi (Perkin Elmer), Model RMU-7, or a Varian, Model M-66, mass spectrometer. All reactions involving strong bases or reactive organometallic intermediates were performed under a nitrogen atmosphere.
17. R. A. Abramovitch and D. L. Struble, Tetrahedron, 24, 357 (1968).
18. The general procedure of S. Dev, J. Indian Chem. Soc., 33, 769 (1956).
19. G. M. Whitesides, C. P. Casey, and J. K. Krieger, J. Amer. Chem. Soc., 93, 1379 (1971).
20. G. B. Kauffman and L. A. Teter, Inorg. Syn., 7, 9 (1963).
21. Washing with aqueous  $NH_3$  was found to be an effective method to ensure complete hydrolysis of  $t-BuC\equiv CCu$ .

22. This solution of  $\text{CH}_2=\text{CHLi}$ , prepared from  $(\text{CH}_2=\text{CH})_4\text{Sn}$  by the procedure of D. Seyferth and M. A. Weiner [J. Amer. Chem. Soc., 83, 3583 (1961)], was not contaminated with mineral oil.
23. R. L. Erskine and E. S. Waight, J. Chem. Soc., 3425 (1960).



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